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(54) Title: ARYL AND HETEROARYL COMPOUNDS USEFUL AS FIBROBLAST GROWTH FACTOR ANTAGONISTS

(57) Abstract

Aryl and heteroaryl compounds, pharmaceutical compositions containing the compounds, and methods for using the pharmaceutical compositions for modulating the activity of the FGF family of peptides are provided. Methods for inhibiting the binding of an FGF peptide to an FGF receptor by contacting the receptor with the aromatic acid are also provided. Methods for treating FGF–mediated disorders by administering effective amounts of one or more of these compounds or pharmaceutically acceptable derivatives thereof that inhibit the activity of one or more FGF peptides are also provided.

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ARYL AND HETEROARYL COMPOUNDS USEFUL AS FIBROBLAST GROWTH FACTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to aryl and heteroaryl compounds, compositions and methods for treatment or prevention of fibroblast growth factor (FGF)-mediated diseases. In particular, the invention relates to the use of triphenylmethane, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothienyl, benzofuryl and benzopyrrolyl compounds as FGF antagonists.

BACKGROUND OF THE INVENTION

Fibroblast growth factors (FGFs) are a family of polypeptide mitogens and are ubiquitous in mammals. FGFs and their corresponding receptors, FGFRs, are widely distributed in tissues throughout the body, i.e., the central and peripheral nervous system, retina, kidneys, and myocardium (see, e.g., Johnson *et al.* Adv. Cancer Res. **1993**, 60, 1), and are expressed during embryogenesis (Kimelman *et al.* Science **1988**, 242, 1053). FGFs exhibit potent mitogenic activity in these areas (see, e.g., Gospodarowicz Nature **1974**, 249, 123), are also mitogenic for mesenchymal, neuronal, and epithelial cells (see. e.g., Johnson *et al.* Molecular and Cellular Biology **1990**, 10, 4728; Gospodarowicz *et al.* Exp. Eye Res. **1977**, 25, 631; Thomas FASEB J. **1987**, 1, 434; Gospodarowicz *et al.* J. Cell Physiol. **1987**, S5, 15) and have been implicated in the processes of cell differentiation and maintenance (see, e.g., Anderson Nature **1988**, 332, 360).

The FGFs consist of a family of peptides, of which ten have been identified (FGF-1 through 10). The first two peptides of this family to be isolated and characterized were FGF-1 and FGF-2, more commonly referred to as aFGF and bFGF, respectively, for their acidic and basic isoelectric points, respectively. aFGF and bFGF were initially isolated

from the bovine pituitary (Gospodarowicz J. Biol. Chem. **1975**, 250, 2515), then from bovine brain (Gospodarowicz *et al.* J. Biol. Chem. **1978**, 253, 3736) and later isolated from human brain (Gimenez-Gallego *et al.* Biochem. Biophys. Res. Comm. **1986**, 135, 541). aFGF and bFGF have common biological properties, including the ability to bind to one or more FGF receptors. They also exhibit 55% homology in their amino acid sequences and are highly conserved among species (i.e., human and bovine bFGF exhibit 98.7% identity (see, e.g., U.S. Patent No. 5,288,855; U.S. Patent No. 5,155,214)). Eight other FGFs have been identified based on these structures (FGF-3 through 10): int-2 (FGF-3) (Moore *et al.* EMBO J. **1986**, 5, 919; Jakobovits *et al.* Proc. Nat. Acad. Sci. USA **1986**, 83, 7806), hst-1/KS-FGF (identified from Kaposi's sarcoma DNA)(FGF-4) (Delli-Bovi *et al.* Cell **1987**, 50, 729; Taira *et al.* Proc. Nat. Acad. Sci. USA **1987**, 84, 2980; Huang *et al.* J. Clin. Invest. **1993**, 91, 1191), FGF-5 (Zhan *et al.* Mol. Cell Biol. **1988**, 8, 3487), FGF-6/Hst-2 (Marics *et al.* Oncogene **1989**, 4, 335), karatinocyte growth factor (KGF)(FGF-7) (Finch *et al.* Science **1989**, 245, 752), FGF-8, FGF-9 and FGF-10 (PCT International Publication Number WO 95/24,414). The structures of aFGF and bFGF have also been determined through single-crystal x-ray diffraction (Eriksson Proc. Nat. Acad. Sci. USA **1991**, 88, 3441; Zhang *et al.* Proc. Nat. Acad. Sci. USA **1991**, 88, 3446; Zhu *et al.* Science **1991**, 251, 90).

Basic FGF is a 16kD, acid- and thermally-sensitive peptide. It is an angiogenic factor causing the migration, proliferation and differentiation of endothelial cells to form blood vessels (see, e.g., Montesano *et al.* Proc. Nat. Acad. Sci. USA **1986**, 83, 7279; Folkman *et al.* Science **1987**, 235, 442). This effect indicates possible therapeutic uses of bFGF for wound healing (Folkman Science **1987**, 235, 442; Buntrock *et al.* Exp. Pathol. **1982**, 21, 62), neovascularization, nerve regeneration,

cartilage repair, and enhancing success of tissue transplantation and of bone graft healing (see, generally, PCT International Publication No. WO 92/12245). FGFs have also been reported to be useful as hypotensive agents for reducing high blood pressure and preventing myocardial infarction and cerebral hemorrhages (Saltis *et al.* Atherosclerosis **1995**, 118, 77; PCT International Publication No. WO 92/08473), for the treatment of ulcers (U.S. Patent No. 5,401,721; U.S. Patent No. 5,175,147), in protecting the retina by inhibiting the release of nitric oxide in retinal inflammatory disorders (Goureau *et al.* Proc. Nat. Acad. Sci. USA **1993**, 90, 1) and as a saporin conjugate in treating other ocular pathologies (Lappi *et al.* Biochem. Biophys. Res. Commun. **1989**, 160, 919; Lappi J. Cell Physiol. **1991**, 147, 17; PCT International Publication No. WO 93/16,734) and vascular injury due to balloon angioplasty, preventing restenosis (U.S. Patent No. 5,308,622; U.S. Patent No. 4,378,347).

bFGF may, however, be harmful in some cases in that cell proliferation and angiogenesis are important aspects of tumor growth and tumor development, rheumatoid arthritis, restenosis, In-Stent restenosis, proliferative diabetic retinopathies and diabetes (see, e.g., Folkman Adv. Cancer Res. **1985**, 43, 175; Melnyk *et al.* Arthritis Rheum. **1990**, 33, 493; Sivalingam Arch. Ophthalmol. **1990**, 108, 869). bFGF also functions as an oncogene in melanoma.

There are many diverse forms of aFGF and bFGF receptors (Hanneken *et al.* Proc. Nat. Acad. Sci. USA **1994**, 91, 9170). FGFs are mediated by high and low affinity receptors: 4 FGF receptor genes have been identified and at least 2 produce multiple mRNA transcripts through alternative splicing of the primary transcript. This splicing creates a large number of forms of the receptors and leads to response of the cell to many FGF family members, i.e., one gene gives FGFR-2 and KGF

receptors, and alternate FGFR-1 splicing gives a 50 fold decrease in bFGF binding with unchanged aFGF binding. Receptor expression is also altered by injury and pathological conditions (restenosis, tumors and proliferative diseases). For example, receptor mRNA and protein are present in melanoma cells (see, e.g., Becker *et al.* Oncogene **1992**, 7, 2303), the receptor message is not usually found in palmar fascia, but is found in the proliferative hand disease Dupuytren's contracture (see, e.g., Gonzales *et al.* Amer. J. Pathol. **1992**, 141, 661), and smooth muscle cells (SMCs) have no response to bFGF, but proliferating SMCs (i.e., during restenosis after balloon angioplasty) strongly respond to bFGF (see, e.g., Casscells *et al.* Proc. Nat. Acad. Sci. USA **1992**, 89, 7159). There are also soluble forms of FGFs in blood, suggesting further activity (Venkateswaran *et al.* Hybridoma **1992**, 11, 729).

These potentially harmful effects of bFGF have led to attempts to identify human bFGF antagonists to treat and/or prevent FGF-mediated diseases. Therefore, it is an object herein to provide antagonists of human bFGF for treatment and/or prevention of FGF-mediated diseases. In particular, it is an object herein to provide aryl and heteroaryl compounds, compositions thereof, and methods of treatment or prevention of FGF-mediated diseases using the compounds and compositions.

SUMMARY OF THE INVENTION

Aryl and heteroaryl compounds, and pharmaceutically acceptable derivatives, including salts, esters, acids bases, solvates, hydrates and prodrugs, thereof, of formulae (I) are provided. Pharmaceutical compositions containing aryl or heteroaryl compounds, or pharmaceutically acceptable derivatives, including salts, esters, acids, bases, solvates, hydrates and prodrugs, thereof, of formulae (I), and methods for modulating the interaction of an FGF peptide with FGF receptors using such compounds and compositions are also provided. In particular,

methods for inhibiting the binding of an FGF peptide to FGF receptors using such compounds and compositions are provided. Among the compounds and pharmaceutical compositions provided herein are those that are particularly active as bFGF antagonists, as evidenced by in vitro assays described herein. The methods are effected by contacting FGF receptors with one or more of the compounds or compositions prior to, simultaneously with, or subsequent to contacting the receptors with an FGF peptide.

The aryl and heteroaryl compounds have formulae (I):

$$Ar^1\text{-}V^1 \quad or \quad Ar^2 = V^2 \qquad (I)$$

where Ar^1 is a monocyclic or fused bicyclic, tricyclic or tetracyclic aromatic or heteroaromatic group, where the heteroaromatic group contains one or two, preferably two, heteroatoms selected from O, S and N; Ar^2 is a monocyclic or fused bicyclic, tricyclic or tetracyclic arylidene or heteroarylidene group, where the heteroarylidene group contains one or two, preferably two, heteroatoms selected from O, S, and N; V^1 is selected from diarylalkyl, diheteroarylalkyl, alkenyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$, $NR^{40}R^{41}$ and $-(CH_2)_k-S(O)_s-R^{70}$, where k is 0-6 and s is 0-2; V^2 is diarylalkylidene, diheteroarylalkylidene or $=NR^{52}$; R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene; R^{52} is aryl, heteroaryl or $NR^{60}R^{61}$; R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl; R^{56} is selected from aryl, heteroaryl and N=heterocyclyl; R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl or $S(O)_m$-aryl or -heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene; and R^{70} is selected from alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl.

In all embodiments, the aryl, heteroaryl, arylidene and heteroarylidene moieties of the compounds of formula (I) are unsubstituted or are substituted with one or more substituents each independently selected from Z, which, as defined herein, is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, hydroxysulfonyl, hydroxyphosphoryl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl, or any two Z groups substituting adjacent atoms may form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene.

In the above compounds, the alkyl, alkynyl and alkenyl portions of each listed substituent are straight or branched chains or are cyclic, and preferably have from about 1 up to about 20 carbons; in more preferred embodiments they have from 1-16 carbons, and they can have fewer than 6 carbons. The carbocyclic, heterocyclic, aromatic and heteroaromatic groups can have from 3 to 19 members in the rings and may be

single or fused rings. The ring size and carbon chain length are selected up to a size such that the resulting molecule retains activity as an FGF antagonist, such that the resulting compound inhibits binding of an FGF peptide, compared to binding in the absence of the aryl or heteroaryl derivative, to an FGF receptor at a concentration of less than about 300 μM.

Of the compounds described herein, those that inhibit an FGF-mediated activity by about 50% at concentrations of less than about 300 μM are preferred. More preferred are those that inhibit an FGF-mediated activity by about 50% at concentrations of less than about 100 μM, more preferably less than about 10 μM, and most preferably less than about 1 μM.

Also of interest are any pharmaceutically-acceptable derivatives, including salts, esters, acids, bases, solvates, hydrates and prodrugs of the aryl and heteroaryl compounds. Pharmaceutically-acceptable salts, include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chloro-benzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates,

malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

Pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable salts, esters, acids, bases, solvates, hydrates or prodrugs, that deliver amounts effective for the treatment of FGF-mediated disorders, and other conditions that are in some manner mediated by an FGF peptide or whose symptoms can be ameliorated by administration of a bFGF-specific FGF antagonist, are also provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the disorders.

Methods for treatment or prevention of FGF-mediated diseases, including, but not limited to, diabetes, cancer, including, but not limited to, melanoma and tumor growth and development, restenosis, In-Stent restenosis, rheumatoid arthritis, proliferative dermatological disorders, and ophthalmic disorders, including, but not limited to, corneal clouding following excimer laser surgery, closure of trabeculectomies, hyperproliferation of lens epithelial cells following cataract surgery, the recurrence of pterygii and diabetic retinopathy, and other proliferative diseases, including, but not limited to, Dupuytren's contracture, conditions that are in some manner mediated by an FGF peptide that binds to FGF receptors, or that are ameliorated by administration of an FGF receptor bFGF antagonist are provided.

Methods for inhibiting binding of an FGF peptide to an FGF receptor are provided. These methods are practiced by contacting the receptor with one or more of the compounds or compositions provided herein simultaneously, prior to, or subsequent to contacting the receptor with an FGF peptide.

In particular, methods of treating FGF-mediated disorders by administering effective amounts of the compounds, or salts, esters, acids, bases, solvates, hydrates, prodrugs or other suitable derivatives thereof are provided. In particular, methods for treating FGF-mediated disorders, including, but not limited to, diabetes, cancer, including, but not limited to, melanoma and tumor growth and development, restenosis, In-Stent restenosis, rheumatoid arthritis, ophthalmic disorders, including, but not limited to, corneal clouding following excimer laser surgery, closure of trabeculectomies, hyperproliferation of lens epithelial cells following cataract surgery, the recurrence of pterygii and diabetic retinopathy, and other proliferative diseases, including, but not limited to, Dupuytren's contracture, and other proliferative diseases in which FGF receptor bFGF-mediated physiological responses are implicated, by administering effective amounts of one or more of the compounds provided herein in pharmaceutically acceptable carriers are provided.

In practicing the methods, effective amounts of compositions containing therapeutically effective concentrations of the compounds formulated for oral, intravenous, local and topical application for the treatment of FGF-mediated disorders, including, but not limited to, diabetes, cancer, including, but not limited to, melanoma and tumor growth and development, restenosis, In-Stent restenosis, rheumatoid arthritis, ophthalmic disorders, including, but not limited to, corneal clouding following excimer laser surgery, closure of trabeculectomies, hyperproliferation of lens epithelial cells following cataract surgery, the recurrence of pterygii and diabetic retinopathy, and other proliferative diseases, including, but not limited to, Dupuytren's contracture, psoriasis, and other diseases in which FGF-mediated physiological responses are implicated are administered to an individual exhibiting the

symptoms of one or more of these disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the disorders.

In addition, methods for identifying compounds that are suitable for use in treating particular diseases based on their preferential affinity for an FGF receptor are also provided.

Articles of manufacture containing packaging material, a compound or composition, or salt, ester, acid, base, solvate, hydrate, or prodrug thereof, provided herein, which is effective for ameliorating the symptoms of an FGF-mediated disorder, antagonizing the effects of bFGF or inhibiting binding of an FGF peptide to an FGF receptor, within the packaging material, and a label that indicates that the compound or composition, or salt, ester, acid, base, solvate, hydrate, or prodrug thereof, is used for antagonizing the effects of bFGF, treating an FGF-mediated disorder, or inhibiting the binding of an FGF peptide to an FGF receptor, are provided.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. Where permissible, all patents and publications referred to herein are incorporated by reference.

As used herein, fibroblast growth factor (FGF) peptides include peptides that have substantially the amino acid sequence of any one of FGF-1 through 10 and that act as potent endogenous proliferative peptides.

As used herein, an FGF-mediated condition is a condition that is caused by abnormal FGF activity or one in which compounds that inhibit FGF activity have therapeutic use. Such diseases include, but are not limited to diabetes, cancer, including, but not limited to, melanoma and

tumor growth and development, restenosis, In-Stent restenosis, rheumatoid arthritis, ophthalmic disorders, including, but not limited to, corneal clouding following excimer laser surgery, closure of trabeculectomies, hyperproliferation of lens epithelial cells following cataract surgery, the recurrence of pterygii and diabetic retinopathy, and other proliferative diseases, including, but not limited to, Dupuytren's contracture, and other diseases in which FGF-mediated physiological responses are implicated.

As used herein an effective amount of a compound for treating a particular disease is an amount that is sufficient to ameliorate, or in some manner reduce the symptoms associated with the disease. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective. The amount may cure the disease but, typically, is administered in order to ameliorate the symptoms of the disease. Typically, repeated administration is required to achieve the desired amelioration of symptoms.

As used herein, an FGF antagonist is a compound, such as a drug or an antibody, that inhibits FGF-stimulated proliferation and other FGF-mediated physiological responses. The antagonist may act by interfering with the interaction of the FGF with an FGF-specific receptor or by interfering with the physiological response to or bioactivity of an FGF isopeptide, such as proliferation. Thus, as used herein, an FGF antagonist interferes with FGF-stimulated proliferation or other response or interferes with the interaction of an FGF peptide with an FGF-specific receptor, such as bFGF receptors, as assessed by assays known to those of skill in the art.

The effectiveness of potential FGF antagonists can be assessed using methods known to those of skill in the art. For example, the effectiveness may be measured by inhibition of binding of ^{125}I-bFGF to a

human extracellular-domain FGFR1-tPA fusion protein immobilized on a solid phase (hsRRA assay)(for the extracellular form of human FGFR, see U.S. Patent 5,288,855). Effectiveness may also be measured through the use of a membrane-bound competitive binding assay, quantifying inhibition of binding of ^{125}I-bFGF to FGF receptors on cultured smooth muscle cells (SMCs). Effectiveness may also be measured by determination of inhibition of ^{3}H-thymidine incorporation into DNA, which is promoted by bFGF stimulation of SMC proliferation (see, generally; Nachtigal *et al.* In Vitro Cellular and Developmental Biology **1989**, 25, 892).

As used herein, the biological activity or bioactivity of an FGF peptide includes any activity induced, potentiated or influenced by FGF in vivo. It also includes the ability to bind to particular receptors and to induce a functional response, such as proliferation. It may be assessed by in vivo assays or by in vitro assays, such as those exemplified herein. The relevant activity includes, but is not limited to, proliferation. Any assay known to those of skill in the art to measure or detect such activity may be used to assess such activity (see, e.g., Nachtigal *et al.* In Vitro Cellular and Developmental Biology **1989**, 25, 892; and the Examples herein).

As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as binding of FGF to tissue receptors, in an assay that measures such response.

As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, acids, bases, solvates, hydrates or prodrugs thereof that may be readily prepared by those of skill in this art using known methods for such derivatization and that produce compounds that may be administered to animals or humans without substantial toxic effects and that either are pharmaceutically active or are prodrugs. For example, acidic groups can be esterified or neutralized.

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use as contraceptive agents.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis and high performance liquid chromatography (HPLC), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such

instances, further purification might increase the specific activity of the compound.

As used herein, biological activity refers to the in vivo activities of a compound or physiological responses that result upon in vivo administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmaceutical activity of such compounds, compositions and mixtures.

As used herein, a prodrug is a compound that, upon in vivo administration, is metabolized or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, e.g., Nogrady (1985) Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392). For example, succinyl-sulfathiazole is a prodrug of 4-amino-N-(2-thiazoyl)benzenesulfonamide (sulfathiazole) that exhibits altered transport characteristics.

As used herein, alkyl, alkenyl and alkynyl carbon chains, if not specified contain from 1 to 20 carbons, preferably 1 to 16 carbons, and are straight or branched. Alkenyl carbon chains of from 2 to 20 carbons preferably contain 1 to 8 double bonds, and the alkenyl carbon chains of 2 to 16 carbons preferably contain 1 to 5 double bonds. Alkynyl carbon chains of from 2 to 20 carbons preferably contain 1 to 8 triple bonds,

and the alkynyl carbon chains of 2 to 16 carbons preferably contain 1 to 5 triple bonds. The alkyl, alkenyl and alkynyl groups may be optionally substituted, with one or more groups, preferably alkyl group substituents that may be the same or different. As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having less than about 6 carbons.

As used herein, an alkyl group substituent includes halo, haloalkyl, preferably halo lower alkyl, aryl, hydroxy, alkoxy, aryloxy, alkyloxy, alkylthio, arylthio, aralkyloxy, aralkylthio, carboxy alkoxycarbonyl, oxo and cycloalkyl.

As used herein, "aryl" refers to cyclic groups containing from 3 to 19 carbon atoms. Aryl groups include, but are not limited to groups, such as phenyl, substituted phenyl, naphthyl, substituted naphthyl, in which the substituent is lower alkyl, halogen, or lower alkoxy.

As used herein, an "aryl group substituent" includes alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl optionally substituted with 1 or more, preferably 1 to 3, substituents selected from halo, halo alkyl and alkyl, arylalkyl, heteroarylalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, halo, hydroxy, haloalkyl and polyhaloalkyl, preferably halo lower alkyl, especially trifluoromethyl, formyl, alkylcarbonyl, arylcarbonyl that is optionally substituted with 1 or more, preferably 1 to 3, substituents selected from halo, halo alkyl and alkyl, heteroarylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylamino-carbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, amino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkylcarbonylamino, arylcarbonyl-amino, azido, nitro, mercapto, alkylthio, arylthio, perfluoroalkylthio,

thiocyano, isothiocyano, alkylsulfinyl, alkylsufonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl and arylaminosulfonyl. Exemplary aryl groups include optionally substituted phenyl and optionally substituted pyrenyl.

As used herein, "cycloalkyl" refers to a saturated mono- or multicyclic ring system, preferably of 3 to 19 carbon atoms, more preferably 3 to 6 carbon atoms; cycloalkenyl and cycloalkynyl refer to mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenyl and cycloalkynyl groups may preferably contain 3 to 19 carbon atoms, with cycloalkenyl groups more preferably containing 4 to 7 carbon atoms and cycloalkynyl groups more preferably containing 8 to 10 carbon atoms. The ring systems of the cycloalkyl, cycloalkenyl and cycloalkynyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion, and may be optionally substituted with one or more alkyl group substituents.

As used herein, "heteroaryl" refers to a monocyclic or multicyclic ring system, preferably of about 3 to about 19 members where one or more, more preferably 1 to 3 of the atoms in the ring system is a heteroatom, that is, an element other than carbon, for example, nitrogen, oxygen and sulfur atoms. The heteroaryl may be optionally substituted with one or more, preferably 1 to 3, aryl group substituents. Exemplary heteroaryl groups include, for example, furyl, thienyl, pyridyl, pyrrolyl, N-methylpyrrolyl, quinolinyl and isoquinolinyl, with pyridyl and quinolinyl being preferred.

As used herein, a "heteroarylium" group is a heteroaryl group that is positively charged on one or more of the heteroatoms.

As used herein, "heterocyclic" refers to a monocyclic or multicyclic ring system, preferably of 3 to 19 members, more preferably

4 to 7 members, even more preferably 5 to 6 members, where one or more, preferably 1 to 3 of the atoms in the ring system is a heteroatom, that is, an element other than carbon, for example, nitrogen, oxygen and sulfur atoms. The heterocycle may be optionally substituted with one or more, preferably 1 to 3 aryl group substituents. Preferred substituents of the heterocyclic group include hydroxy, alkoxy containing 1 to 4 carbon atoms, halo lower alkyl, including trihalomethyl, such as trifluoromethyl, and halogen. As used herein, the term heterocycle may include reference to heteroaryl. Exemplary heterocycles include, for example, pyrrolidinyl, piperidinyl, alkylpiperidinyl, morpholinyl, oxadiazolyl or triazolyl.

As used herein, the nomenclature alkyl, alkoxy, carbonyl, etc. are used as is generally understood by those of skill in this art. For example, as used herein alkyl refers to saturated carbon chains that contain one or more carbons; the chains may be straight or branched or include cyclic portions or be cyclic. As used herein, alicyclic refers to aryl groups that are cyclic.

As used herein, "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, pseudohalides are compounds that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides (X^-, in which X is a halogen, such as Cl or Br). Pseudohalides include, but are not limited to cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethyl and azide.

As used herein, "haloalkyl" refers to a lower alkyl radical in which one or more of the hydrogen atoms are replaced by halogen including, but not limited to, chloromethyl, trifluoromethyl, 1-chloro-2-fluoroethyl and the like.

As used herein, "haloalkoxy" refers to RO- in which R is a haloalkyl group.

As used herein, "sulfinyl" refers to -S(O)-. As used herein, "sulfonyl" refers to $-S(O)_2-$.

As used herein, "aminocarbonyl" refers to $-C(O)NH_2$.

As used herein, "alkylaminocarbonyl" refers to -C(O)NHR in which R is hydrogen or alkyl, preferably lower alkyl. As used herein "dialkylaminocarbonyl" as used herein refers to -C(O)NR'R in which R' and R are independently selected from hydrogen or alkyl, preferably lower alkyl; "carboxamide" refers to groups of formula -NR'COR.

As used herein, "diarylaminocarbonyl" refers to -C(O)NRR' in which R and R' are independently selected from aryl, preferably lower aryl, more preferably phenyl.

As used herein, "arylalkylaminocarbonyl" refers to -C(O)NRR' in which one of R and R' is aryl, preferably lower aryl, more preferably phenyl, and the other of R and R' is alkyl, preferably lower alkyl.

As used herein, "arylaminocarbonyl" refers to -C(O)NHR in which R is aryl, preferably lower aryl, more preferably phenyl.

As used herein, "alkoxycarbonyl" refers to -C(O)OR in which R is alkyl, preferably lower alkyl.

As used herein, "aryloxycarbonyl" refers to -C(O)OR in which R is aryl, preferably lower aryl, more preferably phenyl.

As used herein, "alkoxy" and "alkylthio" refer to RO- and RS-, in which R is alkyl, preferably lower alkyl.

As used herein, "aryloxy" and "arylthio" refer to RO- and RS-, in which R is aryl, preferably lower aryl, more preferably phenyl.

As used herein, "alkylene" refers to a straight, branched or cyclic, preferably straight or branched, bivalent aliphatic hydrocarbon group, preferably having from 1 to about 20 carbon atoms, more preferably 1 to

12 carbons, even more preferably lower alkylene. The alkylene group is optionally substituted with one or more "alkyl group substituents." There may be optionally inserted along the alkylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl as previously described. Exemplary alkylene groups include methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-(CH_2)_3-$), cyclohexylene ($-C_6H_{10}-$), methylenedioxy ($-O-CH_2-O-$) and ethylenedioxy ($-O-(CH_2)_2-O-$). The term "lower alkylene" refers to alkylene groups having 1 to 6 carbons. Preferred alkylene groups are lower alkylene, with alkylene of 1 to 3 carbon atoms being particularly preferred.

As used herein, "alkenylene" refers to a straight, branched or cyclic, preferably straight or branched, bivalent aliphatic hydrocarbon group, preferably having from 2 to about 20 carbon atoms and at least one double bond, more preferably 2 to 12 carbons, even more preferably lower alkenylene. The alkenylene group is optionally substituted with one or more "alkyl group substituents." There may be optionally inserted along the alkenylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl as previously described. Exemplary alkenylene groups include $-CH=CH-CH=CH-$ and $-CH=CH-CH_2-$. The term "lower alkenylene" refers to alkenylene groups having 2 to 6 carbons. Preferred alkenylene groups are lower alkenylene, with alkenylene of 3 to 4 carbon atoms being particularly preferred.

As used herein, "alkynylene" refers to a straight, branched or cyclic, preferably straight or branched, bivalent aliphatic hydrocarbon group, preferably having from 2 to about 20 carbon atoms and at least one triple bond, more preferably 2 to 12 carbons, even more preferably lower alkynylene. The alkynylene group is optionally substituted with

one or more "alkyl group substituents." There may be optionally inserted along the alkynylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl as previously described. Exemplary alkynylene groups include —C≡C—C≡C—, -C≡C- and -C≡C-CH_2-. The term "lower alkynylene" refers to alkynylene groups having 2 to 6 carbons. Preferred alkynylene groups are lower alkynylene, with alkynylene of 3 to 4 carbon atoms being particularly preferred.

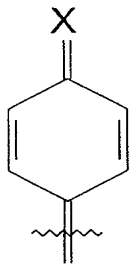
As used herein, "arylene" refers to a monocyclic or polycyclic, preferably monocyclic, bivalent aromatic group, preferably having from 3 to about 20 carbon atoms and at least one aromatic ring, more preferably 3 to 12 carbons, even more preferably lower arylene. The arylene group is optionally substituted with one or more "alkyl group substituents." There may be optionally inserted around the arylene group one or more oxygen, sulphur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl as previously described. Exemplary arylene groups include 1,2-, 1,3- and 1,4-phenylene. The term "lower arylene" refers to arylene groups having 5 or 6 carbons. Preferred arylene groups are lower arylene.

As used herein, "heteroarylene" refers to a bivalent monocyclic or multicyclic ring system, preferably of about 3 to about 15 members where one or more, more preferably 1 to 3 of the atoms in the ring system is a heteroatom, that is, an element other than carbon, for example, nitrogen, oxygen and sulfur atoms. The heteroarylene group may be optionally substituted with one or more, preferably 1 to 3, aryl group substituents. Exemplary heteroarylene groups include, for example, 1,4-imidazolylene.

As used herein, "alkylidene" refers to a bivalent group, such as =CR'R", which is attached to one atom of another group, forming a

double bond. Exemplary alkylidene groups are methylidene ($=CH_2$) and ethylidene ($=CHCH_3$). As used herein, "arylalkylidene" refers to an alkylidene group in which either R' or R" is and aryl group. As used herein, "diarylalkylidene" refers to an alkylidene group in which R' and R" are both aryl groups. "Diheteroarylalkylidene" refers to an alkylidene group in which R' and R" are both heteroaryl groups.

As used herein, "arylidene" refers to an unsaturated cyclic bivalent group where both points of attachment are on the same atom of the ring. Exemplary arylidene groups include, but are not limited to, quinone methide moieties that have the formula:



where X is O, S or NR'. "Heteroarylidene" groups are arylidene groups where one or two, preferably two, of the atoms in the ring are heteroatoms, such as, but not limited to, O, S and N.

As used herein, "amido" refers to a bivalent group, either -C(O)NH- or -HNC(O)-. "Thioamido" refers to a bivalent group, either -C(S)CH- or -HNC(S)-. "Oxyamido" refers to a bivalent group, either -OC(O)NH- or -HNC(O)O-. "Thiaamido" refers to a bivalent group, either -SC(O)NH- or -HNC(O)S-. "Dithiaamido" refers to a bivalent group, either -SC(S)NH- or -HNC(S)S-. "Ureido" refers to the bivalent group -HNCONH-. "Thioureido" refers to the bivalent group -HNCSNH-.

As used herein, the term "amino acid" refers to α-amino acids which are racemic, or of either the D- or L-configuration.

As used herein, when any particular group, such as phenyl or pyridyl, is specified, this means that the group is unsubstituted or is substituted. Preferred substituents where not specified are halo, halo lower alkyl, and lower alkyl.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, Biochem. **1972**, 11, 942).

A. Compounds and derivatives thereof for use in treatment or prevention of FGF-mediated diseases

Compounds and pharmaceutical compositions containing the compounds or pharmaceutically acceptable salts, esters, acids, bases, solvates, hydrates and prodrugs of formulae (I):

$$Ar^1\text{-}V^1 \quad or \quad Ar^2 = V^2 \qquad (I)$$

where Ar^1 is a monocyclic or fused bicyclic, tricyclic or tetracyclic aromatic or heteroaromatic group, where the heteroaromatic group contains one or two, preferably two, heteroatoms selected from O, S and N; Ar^2 is a monocyclic or fused bicyclic, tricyclic or tetracyclic arylidene or heteroarylidene group, where the heteroarylidene group contains one or two, preferably two, heteroatoms selected from O, S, and N; V^1 is selected from diarylalkyl, diheteroarylalkyl, alkenyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$, $NR^{40}R^{41}$ and $-(CH_2)_k-S(O)_s-R^{70}$, where k is 0-6 and s is 0-2; V^2 is diarylalkylidene, diheteroarylalkylidene or $=NR^{52}$; R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene; R^{52} is aryl, heteroaryl or $NR^{60}R^{61}$; R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl; R^{56} is selected

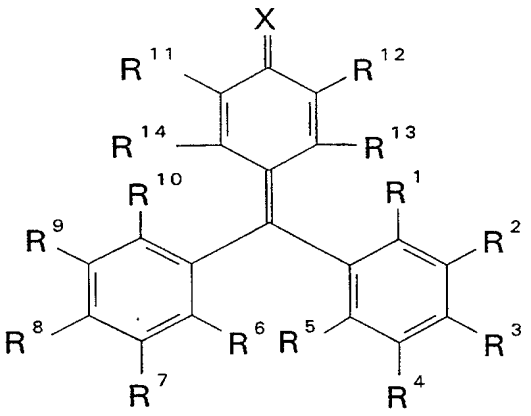
from aryl, heteroaryl and N=heterocyclyl; R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl or $S(O)_m$-aryl or -heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene; and R^{70} is selected from alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl, are provided.

In all embodiments, the aryl, heteroaryl, arylidene and heteroarylidene moieties of the compounds of formula (I) are unsubstituted or are substituted with one or more substituents each independently selected from Z, which, as defined herein, is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, hydroxysulfonyl, hydroxyphosphoryl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkyl-aminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl, or any two Z groups substituting adjacent atoms may form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene.

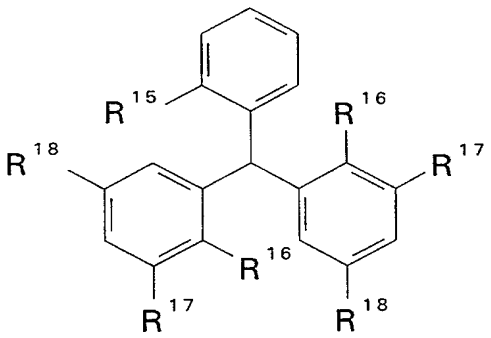
The compounds and compositions are useful as fibroblast growth factor antagonists and in treatment or prevention of FGF-mediated diseases. FGF-mediated diseases that may be treated or prevented using the compounds or compositions provided herein include, but are not limited to, diabetes, cancer, including, but not limited to, melanoma and tumor growth and development, restenosis, In-Stent restenosis, rheumatoid arthritis, proliferative dermatological disorders, ophthalmic disorders, including, but not limited to, corneal clouding following excimer laser surgery, closure of trabeculectomies, hyperproliferation of lens epithelial cells following cataract surgery, the recurrence of pterygii and diabetic retinopathy, and other proliferative diseases, including, but not limited to, Dupuytren's contracture, conditions that are in some manner mediated by an FGF peptide that binds to FGF receptors, or that are ameliorated by administration of an FGF receptor bFGF antagonist.

1. Triarylmethane compounds of formula (II)

In one embodiment, the compounds of formula (I) are triaryl-methane derivatives of formulae (II):



(IIa)



(IIb)

and pharmaceutically acceptable derivatives thereof, where:

R^1 and R^5 are each independently selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$, or, together with R^{13}, form oxy;

R^2 and R^4 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with R^3, form alkylenylamino;

R^3 is hydrogen, hydroxy, thioxy, alkoxy, aryloxy, SR^{40} or $NR^{40}R^{41}$, or, together with R^2 or R^4, forms alkylenylamino;

R^6 and R^{10} are each independently selected from hydrogen, halide, pseudohalide, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$;

R^7 and R^9 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^8 is hydrogen, halide, pseudohalide, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, aryloxy, heteroaryloxy, $NR^{40}R^{41}$, CO_2R^{20}, $PO_3(R^{20})_2$ or SO_nR^{20} where n is 0-3;

R^{11} is selected from hydrogen, halide and pseudohalide, or, together with X, forms alkylenylammonium;

R^{12} is hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with X, forms alkylenylammonium;

R^{13} is hydrogen, or, together with R^1 or R^5, forms oxy;

R^{14} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

X is oxy, thio, NR^{40} or $N^+R^{40}R^{41}$, or, together with R^{11} and/or R^{12}, forms alkylenylammonium;

R^{15} is CO_2R^{20}, SO_3R^{20} or $PO_3(R^{20})_2$;

R^{16} is selected from hydrogen, alkoxy, aralkoxy, heteroaralkoxy, aryloxy and heteroaryloxy;

R^{17} and R^{18} are each independently hydrogen, halide or pseudohalide;

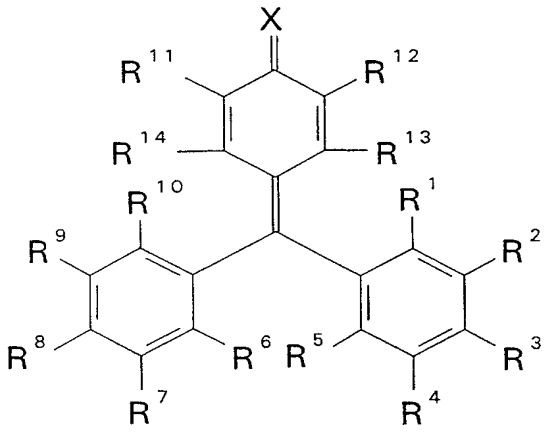
R^{20} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl and Na; and

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene.

In preferred embodiments, the compounds are of formulae (IIa) where R^1-R^{14} and X are selected as above. In these embodiments, the compounds are diphenylmethylidene quinone methides, diphenylmethylidene thiaquinone methides, and imminium derivatives thereof.

a. **Compounds of formula (IIa)**

In particular, preferred compounds of formula (II) have formula (IIa):



(IIa)

where:

R^1 and R^5 are each independently selected from hydrogen, methyl, CO_2Et and Br, or form oxy with R^{13};

R^2 and R^4 are each independently hydrogen, Br or isopropyl, or form propylenylamino with R^3;

R^3 is selected from hydrogen, hydroxy, amino, (4-hydroxysulfonylphenylmethyl)(ethyl)amino and (3-hydroxysulfonylphenylmethyl)(ethyl)amino, or forms propylenylamino with R^2 or R^4;

R^6 and R^{10} are each independently hydrogen, Br or hydroxysulfonyl;

R^7 and R^9 are each independently selected from hydrogen, Br and methyl;

R^8 is hydrogen, hydroxy, Br, hydroxysulfonyl, ethylamino, amino or 4-ethoxyphenylamino;

R^{11} is hydrogen or Br, or forms propylenylammonium with X;

R^{12} is selected from hydrogen, Br and isopropyl, or forms propyleneylammonium with X;

R^{13} is hydrogen or forms oxy with R^1 or R^5;

R^{14} is selected from hydrogen and methyl; and

X is O, NH or (4-hydroxysulfonylphenylmethyl)(ethyl)imminium, or forms propylenylammonium with R^{11} and R^{12}.

Presently preferred compounds of formula (IIa) are triphenylmethane dyes including those where:

X is O; R^1, R^{13} and R^{14} are H; R^2, R^4-R^9, R^{11} and R^{12} are Br; R^3 is OH; and R^{10} is SO_3Na (2-((4-oxo-3,5-dibromo-2,5-cyclohexadien-1-ylidene)(4-hydroxy-3,5-dibromophenyl)methyl)-3,4,5,6-tetrabromophenylsulfonic acid sodium salt or tetabromophenol blue sodium salt);

X is O; R^1 is CO_2Et; R^2-R^6, R^{10}, R^{13} and R^{14} are H; R^7, R^9, R^{11} and R^{12} are Br; and R^8 is OH (ethyl 2-((4-oxo-3,5-dibromo-2,5-cyclohexadien-1-ylidene)(4-hydroxy-3,5-dibromophenyl)methyl)benzoate or 3',3'',5',5''-tetrabromophenolphthalein ethyl ester);

X is O; R^1, R^5-R^9, R^{13} and R^{14} are H; R^2, R^4, R^{11} and R^{12} are Br; R^3 is OH; and R^{10} is SO_3Na (2-((4-oxo-3,5-dibromo-2,5-cyclohexadien-1-

ylidene)(4-hydroxy-3,5-dibromophenyl)methyl)phenylsulfonic acid sodium salt or bromophenol blue sodium salt);

X forms propylenylammonium with R^{11} and R^{12}; R^1, R^6, R^7, R^9 and R^{14} are H; R^2 and R^4 form propylenylamino with R^3; R^5 and R^{13} form O; R^8 is SO_3H; and R^{10} is SO_3Na (2-(9a-aza-2,3,5,7,8,9-hexahydrobenzo-naphtheno[5,4-e]-3a-aza-2,3,4,5,6-pentahydrobenzonaphtheno[9,8-b]-2H-pyran-4-yl)benzene-1,3-disulfonic acid monohydrate or sulforhodamine 101 hydrate);

X is (4-oxysulfonylphenylmethyl)(ethyl)ammonium; R^1, R^2, R^4, R^6, R^7 and R^9-R^{13} are H; R^3 is (4-SO_3Na-phenylmethyl)(ethyl)amino; R^5 and R^{14} are methyl; and R^8 is 4-ethoxyphenylamino (4-((4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)imminium-2-methyl-2,5-cyclohexadien-1-ylidene)(2-methyl-4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)aminophenyl))methyl-N-(4-ethoxyphenyl)aniline sodium salt or brilliant blue G);

X is (4-oxysulfonylphenylmethyl)(ethyl)ammonium; R^1, R^2, R^4-R^7 and R^9-R^{14} are H; R^3 is (4-SO_3Na-phenylmethyl)(ethyl)amino; and R^8 is 4-ethoxyphenylamino (4-((4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)-imminium-2,5-cyclohexadien-1-ylidene)(2-methyl-4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)aminophenyl))methyl-N-(4-ethoxyphenyl)aniline sodium salt or coomassie brilliant blue R-250);

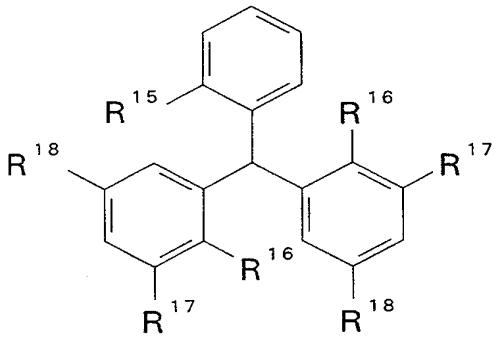
X is (4-oxysulfonylphenylmethyl)(ethyl)ammonium; R^1, R^2, R^4, R^6, R^9-R^{13} are H; R^3 is (4-SO_3Na-phenylmethyl)(ethyl)amino; R^5, R^7 and R^{14} are methyl; and R^8 is ethylamino (4-((4-(N-(4-hydroxysulfonylphenyl)methyl-N-ethyl)imminium-2-methyl-2,5-cyclohexadien-1-ylidene)(2-methyl-4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)aminophenyl))methyl-N-ethyl-2-methylaniline sodium salt or page blue G90);

X is O; R^1, R^6-R^9 and R^{13} are H; R^2 and R^{11} are Br; R^3 is OH; R^4 and R^{12} are isopropyl; R^5 and R^{14} are methyl; and R^{10} is SO_3Na (2-((4-oxo-3-bromo-5-isopropyl-2-methyl-2,5-cyclohexadien-1-ylidene)(3-bromo-4-hydroxy-5-isopropyl-2-methylphenyl)methyl)phenylsulfonic acid sodium salt or bromothymol blue sodium salt); and

X is NH; R^1, R^2, R^4-R^6 and R^9-R^{14} are H; R^3 and R^8 are amino; and R^7 is methyl (4-((4-aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl)-2-methylaniline hydrochloride or fuchsine).

b. Compounds of formula (IIb)

Preferred compounds of formula (II) have formula (IIb):



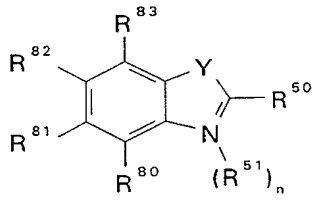
(IIb)

where R^{15} is methoxycarbonyl or hydroxysulfonyl; R^{16} is selected from hydrogen, ethoxy and methoxy; and R^{17} and R^{18} are each selected from hydrogen and Cl.

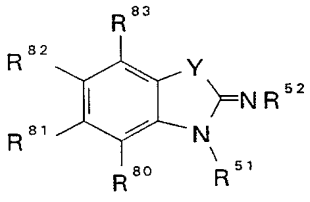
Presently preferred compounds of formula (IIb) include methyl 2-benzydrylbenzoate, α,α-bis(3,5-dichloro-2-ethoxyphenyl)-ortho-toluenesulfonic acid sodium salt and α,α-bis(3,5-dichloro-2-methoxyphenyl)-ortho-toluenesulfonic acid sodium salt.

2. Heteroaryl compounds of formula (III)

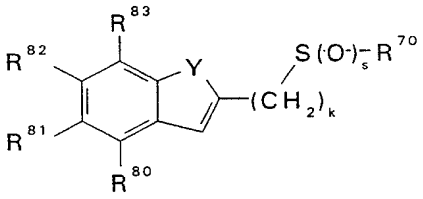
In another embodiment, the compounds of formula (I) are heteroaryl derivatives of formulae (III):



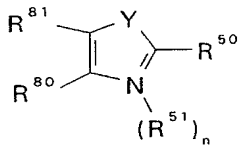
(IIIa)



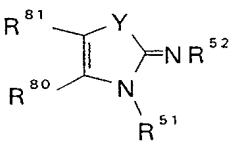
(IIIb)



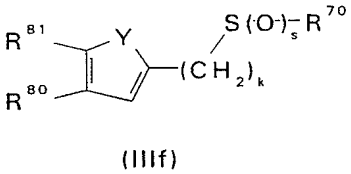
(IIIc)



(IIId)



(IIIe)



(IIIf)

and pharmaceutically acceptable derivatives thereof, where:

Y is O, S or NR^{40};

R^{50} is alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, (N-alkyl-, alkenyl-, hydroxyalkyl- or hydroxycarbonylalkyl-heteroarylium)alkyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, -N=N-R^{56} or $NR^{40}R^{41}$;

R^{51} is selected from hydrogen, alkyl, alkenyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

n is 0 or 1;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is selected from aryl, heteroaryl and $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is aryl, heteroaryl or N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl or $S(O)_m$-aryl or -heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z, preferably from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene which are unsubstituted or substituted with 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i);

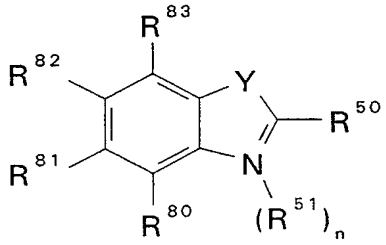
k is 0-6; and s is 0-2.

In embodiments where n is 1, the nitrogen atom of formula (IIIa) or (IIId) is positively charged and the compounds are heteroarylium compounds, such as benzoxazolium, benzothiazolium and benzimidazolium compounds. In these embodiments, a counterion may be present, forming a salt with the positively-charged nitrogen of the heteroarylium group. Such counterions include, but are not limited to, halide, sulfate, tetrahaloborate and perchlorate.

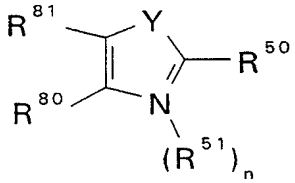
In embodiments where n is 0, R^{51} is absent from formula (IIIa) and (IIId), and the nitrogen atom is neutral. In such embodiments, the compounds are heteroaryl compounds, such as benzoxazoles, benzothiazoles and benzimidazoles.

a. Compounds of formulae (IIIa) and (IIId)

In a preferred embodiment, the compounds of formula (I) are of formulae (IIIa) and (IIId):



(IIIa)



(IIId)

where:

Y is O, S or NR^{40};

R^{50} is alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, (N-alkyl-, alkenyl-, hydroxyalkyl- or hydroxycarbonylalkyl-heteroarylium)alkyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$ or $NR^{40}R^{41}$;

R^{51} is selected from hydrogen, alkyl, alkenyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl, heteroaralkyl, aryl and heteroaryl, preferably from alkyl, alkenyl, hydroxycarbonylalkyl and hydroxyalkyl;

n is 0 or 1;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is aryl, heteroaryl or N=heterocyclyl; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z, preferably from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i).

In more preferred embodiments, the compounds have formulae (IIIa) or (IIId) where:

Y is O, S or ethylamino;

R^{50} is selected from 3-(N-propyl-2-benzothiazolium)prop-1-yl, 3-(N-(2-hydroxy-1-ethyl)-2-benzothiazolium)prop-1-yl, 3-(N-(2-propen-1-yl)-2-benzothiazolium)prop-1-yl, 3-(N-(3-hydroxycarbonyl-1-propyl)-2-benzothiazolium)prop-1-yl, 2-(4-dimethylaminophenyl)ethenyl, 3-(N-ocatadecylbenzoxazol-2-inylidene)propenyl, 2-ethyl-3-(N-ethylnaphtho-thiazol-2-inylidene)propenyl, 2-(N-acetyl-N-phenylamino)ethenyl, (N-methylbenzothiazolin-2-ylidene)aminoazo, 2-(5-(2-(5-chloro-N-ethylbenzo-thiazolin-2-ylidene)ethylidenyl)-1-diphenylamino-1-cyclopenten-2-yl)ethenyl, 2-hydroxypropenyl, 4-dimethylaminophenyl, 2-methyl-3-(N-ethylnaphthothiazol-2-inylidene)propenyl, (N,N'-dimethylbenzimidazolin-2-ylidene)aminoazo, 3-(N,N'-diethyl-5-cyanobenzimidazolin-2-ylidene)-propenyl, 3-ethoxy-1H-phenalen-1-ylidenemethyl, 3-(N-ethylbenzothia-zolin-2-ylidene)-2-methylpropenyl, 3-(N-ethylbenzothiazolin-2-ylidene)-propenyl, 5-(N-ethylbenzothiazolin-2-ylidene)pentadienyl, 2-amino-1-naphthylazo, 4-phenylaminophenylazo, pentamethylphenylmethylthio, 4-(bis(2-hydroxyethyl)amino)phenylazo, phenylmethoxy, 4-(3-(4-(N-benzo-thiazol-2-yl)piperidinyl)propyl)piperidinyl, 2-(4-methylphenylsulfonyl)-aminophenyl, benzothiazol-2-yldithio, 3-(N-(2-propen-1-yl)benzothiazolin-2-ylidene)propenyl, 5-(N-propylbenzothiazolin-2-ylidene)pentadienyl and 6-amino-1,4-dihydro-3-cyano-4-(4-cyanophenyl)-benzothiazolin[2,3-a]pyr-idin-5-yl;

R^{51} is methyl, ethyl, propyl, 2-propen-1-yl, 2-hydroxy-1-thyl, octadecyl or 3-hydroxycarbonyl-1-propyl;

n is 0 or 1; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from hydrogen, methyl, methoxy and Cl; or

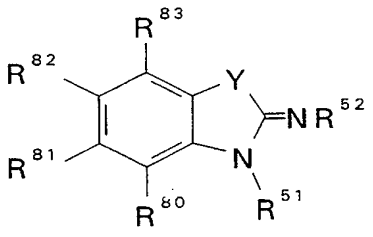
(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene and the others are selected as in (i).

Among the presently preferred compounds of formulae (IIIa) and (IIId) are N-ethyl-2-(2-(4-dimethylaminophenyl)ethenyl)naphtho[2,1-d]thiazolium iodide, 3,3'-dioctadecyloxacarbocyanine perchlorate, N-ethyl-2-(2-ethyl-3-(N-ethylnaphtho[1,2-d]thiazolidin-2-ylidene)propenyl)naphtho[1,2-d]thiazolium bromide, N,N'-dioctadecyloxacarbocyanine para-toluenesulfonate, 2-(2-acetanilinovinyl)-3-ethylbenzothiazolium iodide, 3-methyl-2-((3-methyl-2-benzothiazolinylidene)aminoazo)benzothiazolium tetrafluoroborate, 5-chloro-N-ethyl-2-(2-(5-(2-(5-chloro-N-ethylbenzothiazolin-2-ylidene)ethylidenyl)-1-diphenylamino-1-cyclopenten-2-yl)ethenyl)benzothiazolium perchlorate, N-ethyl-2-(2-hydroxypropen-1-yl)benzothiazolium chloride, 3,6-dimethyl-2-(4-dimethylaminophenyl)benzothiazolium bromide, N-ethyl-2-(2-methyl-3-(N-ethylnaphtho[1,2-d]thiazolidin-2-ylidene)propenyl)naphtho[1,2-d]thiazolium bromide, 2-(4-dimethylamino)-styryl)-3-ethylbenzothiazolium iodide, N-methyl-2-((N,N'-dimethylbenzimidazolin-2-ylidene)aminoazo)benzothiazolium perchlorate, 1-ethyl-2-(3-(N,N'-diethyl-5-cyanobenzimidazolin-2-ylidene)propenyl)-3-(4-hydroxysulfonyl-1-butyl)benzimidazole, 2-(3-ethoxy-1H-phenalen-1-ylidenemethyl)-3-ethylbenzothiazolium tetrafluoroborate, 3,3'-diethyl-9-methylthiacarbocyanine iodide, 3,3'-diethylthiacarbocyanine iodide, 3,3'-diethylthiadicarbocyanine iodide, 3-methyl-2-bromothiazolinone (1,2-dihydro-2-imino-1-naphthylidene)hydrazone hydroiodide, 2-(4-phenylaminophenylazo)-N-methylbenzothiazolium iodide, 2-(pentamethylphenyl)methylthiobenzothiazole, 2-(4-(bis(2-hydroxyethyl)amino)phenylazo)-7-methoxybenzothiazole, 2-

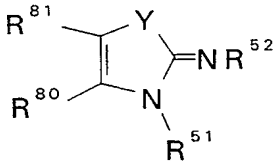
phenylmethoxybenzothiazole, 2-(4-(3-(4-(N-benzothiazol-2-yl)piperidinyl)propyl)piperidinyl)benzothiazole, 2-(2-(4-methylphenyl-sulfonyl)aminophenyl)naphtho[2,3-d]oxazole, bis(2-benzothiazolyl) disulfide, 3,3'-di(2-propen-1-yl)thiacarbocyanine iodide, 3,3'-dipropylthiadicarbocyanine iodide and 2-(6-amino-1,4-dihydro-3-cyano-4-(4-cyanophenyl)-benzothiazolin[2,3-a]pyridin-5-yl)benzothiazole.

b. Compounds of formulae (IIIb) and (IIIe)

In a preferred embodiment, the compounds of formula (I) are of formulae (IIIb) or (IIIe):



(IIIb)



(IIIe)

where:

Y is O, S or NR^{40};

R^{51} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

R^{52} is selected from aryl, heteroaryl and $NR^{60}R^{61}$;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl or $S(O)_m$-aryl or -heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z, preferably from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

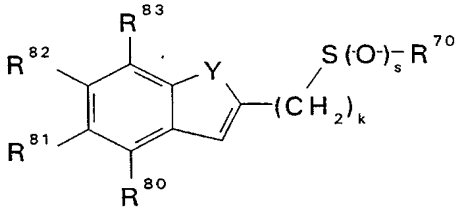
(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i).

In more preferred embodiments, the compounds are of formulae (IIIb) or (IIIe) where Y is S; R^{51} is methyl or ethyl; R^{52} is (4-nitrophenylazo)(phenyl)methylimino, 2-imino-5,6-benzo-3-cyclohexen-1-ylimino, 4-dimethylaminophenyl, 3,4-propylenylphenylmethylimino, 1-(3-aminophenyl)ethylimino, 4-dimethylaminophenylmethylimino or 2-nitrophenylsulfonylamino; and R^{80}, R^{81}, R^{82} and R^{83} are all hydrogen.

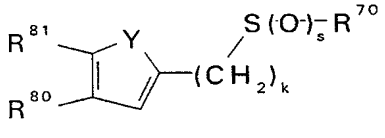
Presently most preferred compounds of formulae (IIIb) and (IIIe) include 4-nitrophenylazobenzoyl N-methylbenzothiazolidinone hydrazine bishydrazone, 2-imino-5,6-benzo-3-cyclohexenone N-methylbenzothiazolidinone hydrazine bishydrazone, N-ethylbenzothiazolidinone 4-dimethylaminophenylimine, 3,4-propylenylbenzaldehyde N-methylbenzothiazolidinone hydrazine bishydrazone, 3-aminoacetophenone N-methylbenzothiazolidinone hydrazine bishydrazone, 4-dimethylaminobenzaldehyde N-methylbenzothiazolidinone hydrazine bishydrazone or N-methylbenzothiazolidinone 2-nitrophenylsulfonylhydrazone.

c. Compounds of formulae (IIIc) and (IIIf)

In a preferred embodiment, the compounds of formula (I) are of formulae (IIIc) and (IIIf):



(IIIc)



(IIIf)

where:

Y is O, S or NR^{40};

R^{70} is alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z, preferably from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i);

k is 0-6; and s is 0-2.

In more preferred embodiments, k is 1 and s is 0 or 2.

In particularly preferred embodiments, the compounds have formulae (IIIc) or (IIIf) where Y is O; R^{70} is aryl; R^{80}, R^{81}, R^{82} and R^{83} are all halide or pseudohalide; k is 1 and s is 0 or 2. More preferably, Y is O, R^{70} is selected from 3-trifluoromethylphenyl, 4-chlorophenyl and 4-methoxyphenyl; R^{80}, R^{81}, R^{82} and R^{83} are all fluoro; k is 1 and s is 0 or 2.

Presently most preferred compounds of formulae (IIIc) and (IIIf) are 2-(3-trifluoromethylphenylthiomethyl)-4,5,6,7-tetrafluorobenz[d]oxazole, 2-(4-chlorophenylsulfonylmethyl)-4,5,6,7-tetrafluorobenz[d]oxazole and 2-(4-methoxyphenylthiomethyl)-4,5,6,7-tetrafluorobenz[d]oxazole.

3. Aryl and heteroaryl derivatives

Also of interest are any pharmaceutically-acceptable derivatives, including salts, esters, acids, bases, solvates, hydrates and prodrugs of the aryl and heteroaryl compounds. In certain embodiments, these derivatives are preferred for use in the compositions and methods. Such derivatives may be prepared by methods known to those of ordinary skill in the art. Pharmaceutically-acceptable salts, include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-

benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethyl-benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

B. Preparation of the compounds

The preparation of the above compounds is described below. Any such compound or similar compound may be synthesized according to a method discussed in general below or by only minor modification of the methods by selecting appropriate starting materials. Additionally, certain compounds described herein may be obtained from commercial sources known to those of skill in the art (e.g., Aldrich Chemical Co., Milwaukee, WI; Sigma, St. Louis, MO; and Fluka Chemical Corporation, Milwaukee, WI).

1. Preparation of the triarylmethane compounds of formula (II)

Triarylmethane compounds of formula (II) may be prepared by the methods described below, by minor modification of the methods described below or by any other methods known to those of skill in the art.

For example, the methods described in U.S. Patent Nos. 5,043,013 and 5,659,053, European Patent application Nos. 491,256, 527,649 and 564,930, German Patent Nos. 2,334,918, 2,555,747 and

4,211,783, and Japanese Patent Nos. 4,261,139, 57,038,856, 58,100,862 and 63,208,559.

Specifically, certain of the compounds of formula (II) may be prepared by oxidation of compounds of formula $(aryl^1)(aryl^2)(aryl^3)CH$ in the presence of a diluent, such as water, glacial acetic acid, chloroform, toluene, N,N-dimethylformamide, N-methylpyrrolidinone, alcohols, glycols or mixtures thereof, and an oxygen transfer catalyst that is a heavy metal (such as, but not limited to, Mn, Fe, Cu, or Cr) complex of a porphyrin, tetraaza[14]annulene, phthalocyanine, or tetraazacyclodecane, or molybdic acid and vanadium in the form of VO_2^+ as catalyst.

Suitable oxidants include, but are not limited to, H_2O_2, a H_2O_2 donor compound, an organic hydroperoxide or peroxide, such as tert-butyl hydroperoxide or benzoyl peroxide, peroxomonosulfuric acid or its salts, benzoquinones, including chloranil, or a percarboxylic acid, or MnO_2 in the presence of an aqueous acid.

Thus, for preparation of certain embodiments of the compounds of formula (II), an aqueous solution of the Na salt of a compound of the above formula where aryl is substituted with $alkylSO_3H$ may be mixed with 5,14-dihydrodibenzo[b,i][5,9,14,18]tetraaza[14]annulene Fe complex, $(H_2O_3PCH_2)_2NCH_2CH_2N(CH_2PO_3H_2)_2$, N-methylimidazole, and finally dropwise with 30% H_2O_2 at 80 °C and stirred 1 h at 60 °C and filtered to give the desired compounds of formula (II).

In other embodiments, the compounds of formula (II) are xanthene derivatives. These compounds may be prepared by ring closure of the appropriate alkoxy-substituted triphenylmethane derivative at 150 °C and pH<7.

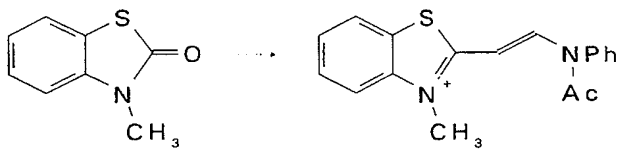
The compounds of formula $(aryl^1)(aryl^2)(aryl^3)CH$ may be synthesized by reaction of the corresponding benzhydryl compounds (e.g., $(aryl^1)(aryl^2)CHOH$) with $aryl^3H$ under acidic conditions.

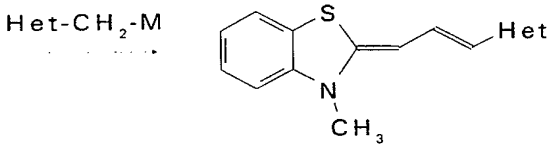
2. Preparation of the heteroaryl compounds of formula (III)

Heteroaryl compounds of formula (III) may be prepared by the methods described below, by minor modification of the methods described below or by any other methods known to those of skill in the art.

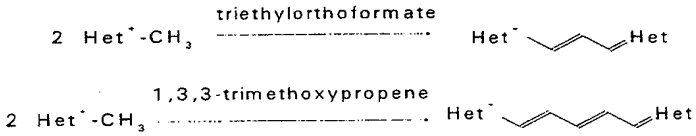
For example, the methods described in U.S. Patent Nos. 5,688,966, 5,679,795 and 5,326,876, European Patent application Nos. EP 800,083, EP 784,233, EP 747,448, EP 730,008 and EP 591,820, International Patent application Publication Nos. WO 96/00902 and WO 94/24213, Japanese Patent Nos. JP 10,036,361, JP 08,269,009, JP 08,104,689 and JP 06,234,755, and German Patent Nos. DE 19,526,499, DE 4,403,083 and DE 4,331,162 may be used to prepare the desired compounds.

Specifically, a heterocyclic ketone, such as, but not limited to, thiazolidinone, oxazolidinone, benzothiazolidinone or benzoxazolidinone, is converted to the corresponding 2-vinylheteroarylium compound that is substituted on the β atom of the vinyl group with, for example, acetanilido. This transformation may use the corresponding 2-alkylthio or alkoxyheteroarylium compound as an intermediate. Reaction of this compound with the anion of a heteroarylmethane results in conjugate addition followed by elimination of acetanilide to provide the desired compounds. This synthetic route is illustrated below for benzothiazolidinone.

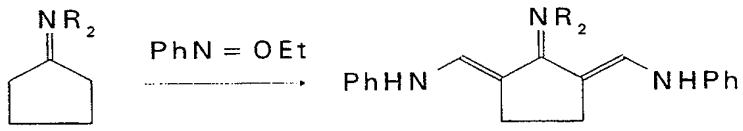


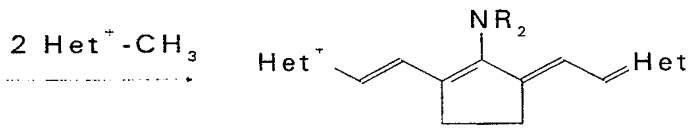


Alternatively, reaction of two equivalents of a 2-methylheteroarylium compound with trialkylorthoformate or 1,3,3-trialkoxypropene provides compounds of formula (III). The requisite 2-methylheteroarylium compound is prepared by N-alkylation of the corresponding 2-methylheteroaryl compound. This synthetic scheme may be represented as follows:



A third method for preparation of compounds of formula (III) involves reaction of a dimethyleneketone imine with PhN=CHOEt, affording a diaminovinylimine. Reaction of this compound with a 2-methylheteroarylium ion affords the desired compounds of formula (III). The reaction scheme is illustrated below.





Other methods include reaction a 2-methylheteroarylium salt with aldehydes or aldehyde derivatives and active methylene compounds. For example, 1-ethyl-2-methyl-1H-benzimidazolium chloride may be condensed (2:1) with 2-chloro-3-(hydroxymethylene)-1-cyclopentene-carboxaldehyde, obtained from cyclopentanone, CH_2Cl_2 and $POCl_3$ in DMF, to give the desired compounds.

C. Evaluation of the bioactivity of the compounds

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess any biological activities of compounds that interfere with or inhibit FGF peptides. Numerous assays are known to those of skill in the art for evaluating the ability of compounds to modulate the activity of one or more FGF peptides. For example, the properties of a potential antagonist may be assessed as a function of its ability to inhibit FGF activity including the ability in vitro to compete for binding to FGF receptors present on the surface of tissues or recombinant cell lines, cell-based competitive assays (see, e.g., Moscatelli *et al.* J. Cell. Physiol. **1987**, 131, 123-130); mitogenic assays (Gospardarowicz *et al.* Proc. Natl. Acad. Sci. U.S.A. **1984**, 81, 6963-6967; Thomas *et al.* Proc. Natl. Acad. Sci. U.S.A. **1984**, 81, 357); stimulation of angiogenesis in vitro (see, e.g., European Patent Application No. EP 645 451); cell proliferation assays or heparin binding assays (see, e.g., International Application Publication No. WO 92/12245); assays measuring the release of cellular proteases (Moscatelli *et al.* Proc. Natl. Acad. Sci. U.S.A. **1986**, 83, 2091-2095; Phadke Biochem. Biophys. Res. Comm. **1987**, 142, 448-453); and, assays for the promotion of FGF-mediated neurite outgrowth and neuron survival (Togari *et al.* Biochem. Biophys. Res. Comm. **1983**, 114, 1189-1193; Wagner *et al.* J. Cell Biol. **1986**, 103, 1363-1367).

In addition, FGF isotype specific antagonists may be identified by the ability of a test compound to interfere with one or more FGF peptide binding to different tissues or cells expressing different endothelin receptor subtypes, or to interfere with the biological effects of an FGF peptide (see, e.g., International Patent Application Publication No. WO 95/24414).

Using such assays, the relative affinities of the compounds for FGF receptors have been and can be assessed. Those that possess the desired in vitro properties, such as specific inhibition of the binding of bFGF, are selected. The selected compounds that exhibit desirable activities may be therapeutically useful in the methods described herein and are tested for such uses employing the above-described assays from which the in vivo effectiveness may be evaluated (Gospodarowicz *et al.* Endocrin. Rev. **1987**, 8, 95-114; Buntrock *et al.* Exp. Pathol. **1982**, 21, 62-67; International Patent Application Publication No WO 92/08473). Compounds that exhibit the in vitro activities that correlate with the in vivo effectiveness will then be formulated in suitable pharmaceutical compositions and used as therapeutics.

An assay that has been used to assess interaction of bFGF with its native receptor is exemplified herein (see, also, Zhu et al. (1995) J. Biol. Chem. 270:21869-21874). This assay can be used to identify compounds provided herein that may be therapeutically useful for treating FGF-mediated disorders.

D. Formulation of pharmaceutical compositions and compounds for use in the methods

Compositions for use in the methods herein contain therapeutically effective amounts of one or more of the compounds of formula (I). The compounds are preferably formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets,

pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures known in the art (see, e.g., Ansel Introduction to Pharmaceutical Dosage Forms, Fourth Edition **1985**, 126).

In the formulations, effective concentrations of one or more compounds or pharmaceutically acceptable derivatives is (are) mixed with a suitable pharmaceutical carrier or vehicle. The compounds may be derivatized as the corresponding salts, esters, acids, bases, solvates, hydrates and prodrugs of the aromatic acids prior to formulation, as described above. The concentrations of the compounds in the formulations are effective for delivery of an amount, upon administration, that ameliorates the symptoms of the FGF-mediated disease. Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome

formulations may be prepared as described in U.S. Patent No. 4,522,811.

The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known in vitro and in vivo systems (see, e.g., Moscatelli *et al.* J. Cell. Physiol. **1987**, 131, 123-130; Gospardarowicz *et al.* Proc. Natl. Acad. Sci. U.S.A. **1984**, 81, 6963-6967; Thomas *et al.* Proc. Natl. Acad. Sci. U.S.A. **1984**, 81, 357; European Patent Application No. EP 645 451; International Application Publication No. WO 92/12245; Moscatelli *et al.* Proc. Natl. Acad. Sci. U.S.A. **1986**, 83, 2091-2095; Phadke Biochem. Biophys. Res. Comm. **1987**, 142, 448-453; Togari *et al.* Biochem. Biophys. Res. Comm. **1983**, 114, 1189-1193; and Wagner *et al.* J. Cell Biol. **1986**, 103, 1363-1367) and then extrapolated therefrom for dosages for humans.

The concentration of active compound in the drug composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to treat the symptoms of diabetes.

Typically a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50-100 μg/ml. The pharmaceutical compositions typically should provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1000 mg

and preferably from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

Preferred pharmaceutically acceptable derivatives include acids, salts, esters, hydrates, solvates and prodrug forms. The derivative is selected such that its pharmacokinetic properties are superior to the corresponding neutral compound.

Thus, effective concentrations or amounts of one or more of the compounds provided herein or pharmaceutically acceptable derivatives thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating or treating the FGF-mediated disorder for which treatment is contemplated. The concentration of active compound in the composition will depend on absorption, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

The compositions are intended to be administered by an suitable route, which includes orally, parenterally, rectally and topically and locally depending upon the disorder being treated. For oral administration, capsules and tablets are presently preferred. The compounds in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. Preferred modes of administration include parenteral and oral modes of administration.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using co-solvents, such as dimethylsulfoxide (DMSO), using surfactants, such as Tween®, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

Upon mixing or addition of the compound with the vehicle, the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors,

including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. If necessary, pharmaceutically acceptable salts or other derivatives of the compounds may be prepared.

The compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. It is understood that number and degree of side effects depends upon the condition for which the compounds are administered. For example, certain toxic and undesirable side effects are tolerated when treating life-threatening illnesses, such as tumors, that would not be tolerated when treating disorders of lesser consequence. The concentration of compound in the composition will depend on absorption, inactivation and excretion rates thereof, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

The formulations are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or

multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

The composition can contain along with the active ingredient: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acaciagelatin, glucose, molasses, polvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan

monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound in an amount sufficient to alleviate the symptoms of the treated subject.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these formulations are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% active ingredient, preferably 0.1-85%, typically 75-95%.

The active compounds or pharmaceutically acceptable derivatives may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

The formulations may be include other active compounds to obtain desired combinations of properties. The compounds of formula (I) or pharmaceutically acceptable derivatives thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as beta-adrenergic blocker (for example atenolol), a calcium channel blocker (for example nifedipine), an angiotensin converting enzyme (ACE) inhibitor (for example lisinopril), a diuretic (for example furosemide or hydrochlorothiazide), an endothelin converting enzyme (ECE) inhibitor (for example phosphoramidon), a neutral endopeptidase (NEP) inhibitor, an HMGCoA reductase inhibitor, a nitric oxide donor, an anti-oxidant, a vasodilator, a dopamine agonist, a neuroprotective agent, a steroid, a beta-agonist, an anti-coagulant, or a thrombolytic agent. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

1. Aryl and heteroaryl compounds and derivatives thereof for use in the compositions and methods

Compounds and pharmaceutical compositions containing the compounds or pharmaceutically acceptable salts, esters, acids, bases, solvates, hydrates and prodrugs of formulae (I):

$$Ar^1\text{-}V^1 \quad \text{or} \quad Ar^2 = V^2 \qquad (I)$$

where Ar^1 is a monocyclic or fused bicyclic, tricyclic or tetracyclic aromatic or heteroaromatic group, where the heteroaromatic group contains one or two, preferably two, heteroatoms selected from O, S and N; Ar^2 is a monocyclic or fused bicyclic, tricyclic or tetracyclic arylidene or heteroarylidene group, where the heteroarylidene group contains one or two, preferably two, heteroatoms selected from O, S,

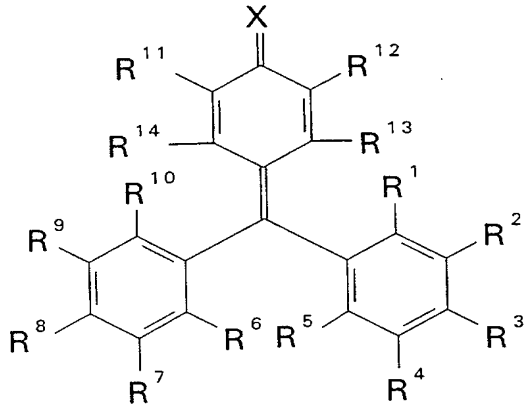
and N; V^1 is selected from diarylalkyl, diheteroarylalkyl, alkenyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, -N=N-R^{56}, $NR^{40}R^{41}$ and -$(CH_2)_k$-$S(O)_s$-R^{70}, where k is 0-6 and s is 0-2; V^2 is diarylalkylidene, diheteroarylalkylidene or $=NR^{52}$; R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene; R^{52} is aryl, heteroaryl or $NR^{60}R^{61}$; R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl; R^{56} is selected from aryl, heteroaryl and N=heterocyclyl; R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl or $S(O)_m$-aryl or -heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene; and R^{70} is selected from alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl, are provided for use in the methods.

In all embodiments, the aryl, heteroaryl, arylidene and heteroarylidene moieties of the compounds of formula (I) are unsubstituted or are substituted with one or more substituents each independently selected from Z, which, as defined herein, is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, hydroxysulfonyl, hydroxyphosphoryl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino,

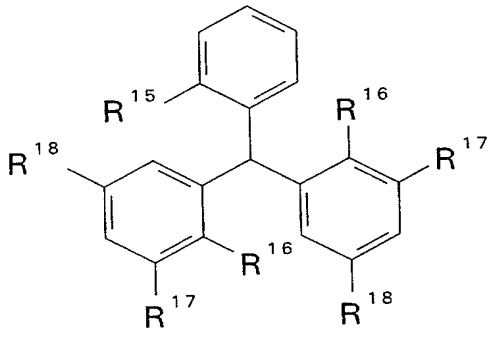
alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl, or any two Z groups substituting adjacent atoms may form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene.

a. Triarylmethane Compounds

In one embodiment, the compounds of formula (I) are triarylmethane derivatives of formulae (II):



(IIa)



(IIb)

and pharmaceutically acceptable derivatives thereof, where:

R^1 and R^5 are each independently selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$, or, together with R^{13}, form oxy;

R^2 and R^4 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with R^3, form alkylenylamino;

R^3 is hydrogen, hydroxy, thioxy, alkoxy, aryloxy, SR^{40} or $NR^{40}R^{41}$, or, together with R^2 or R^4, forms alkylenylamino;

R^6 and R^{10} are each independently selected from hydrogen, halide, pseudohalide, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$;

R^7 and R^9 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^8 is hydrogen, halide, pseudohalide, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, aryloxy, heteroaryloxy, $NR^{40}R^{41}$, CO_2R^{20}, $PO_3(R^{20})_2$ or SO_nR^{20} where n is 0-3;

R^{11} is selected from hydrogen, halide and pseudohalide, or, together with X, forms alkylenylammonium;

R^{12} is hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with X, forms alkylenylammonium;

R^{13} is hydrogen, or, together with R^1 or R^5, forms oxy;

R^{14} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

X is oxy, thio, NR^{40} or $N^+R^{40}R^{41}$, or, together with R^{11} and/or R^{12}, forms alkylenylammonium;

R^{15} is CO_2R^{20}, SO_3R^{20} or $PO_3(R^{20})_2$;

R^{16} is selected from hydrogen, alkoxy, aralkoxy, heteroaralkoxy, aryloxy and heteroaryloxy;

R^{17} and R^{18} are each independently hydrogen, halide or pseudohalide;

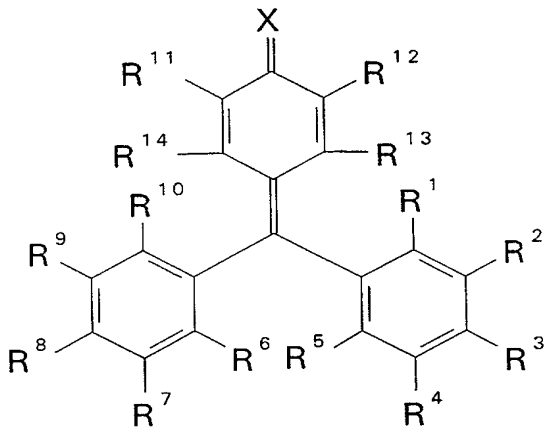
R^{20} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl and Na; and

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene.

In preferred embodiments, the compounds are of formulae (IIa) where R^1-R^{14} and X are selected as above. In these embodiments, the compounds are diphenylmethylidine quinone methides, diphenylmethylidene thiaquinone methides, and imminium derivatives thereof.

i. Compounds of formula (IIa)

In particular, preferred compounds of formula (II) have formula (IIa):



(IIa)

where:

R^1 and R^5 are each independently selected from hydrogen, methyl, CO_2Et and Br, or form oxy with R^{13};

R^2 and R^4 are each independently hydrogen, Br or isopropyl, or form propylenylamino with R^3;

R^3 is selected from hydrogen, hydroxy, amino, (4-hydroxysulfonyl-phenylmethyl)(ethyl)amino and (3-hydroxysulfonylphenylmethyl)(ethyl)-amino, or forms propylenylamino with R^2 or R^4;

R^6 and R^{10} are each independently hydrogen, Br or hydroxysulfonyl;

R^7 and R^9 are each independently selected from hydrogen, Br and methyl;

R^8 is hydrogen, hydroxy, Br, hydroxysulfonyl, ethylamino, amino or 4-ethoxyphenylamino;

R^{11} is hydrogen or Br, or forms propylenylammonium with X;

R^{12} is selected from hydrogen, Br and isopropyl, or forms propyleneylammonium with X;

R^{13} is hydrogen or forms oxy with R^1 or R^5;

R^{14} is selected from hydrogen and methyl; and

X is O, NH or (4-hydroxysulfonylphenylmethyl)(ethyl)imminium, or forms propylenylammonium with R^{11} and R^{12}.

Presently preferred compounds of formula (IIa) are triphenylmethane dyes including those where:

X is O; R^1, R^{13} and R^{14} are H; R^2, R^4-R^9, R^{11} and R^{12} are Br; R^3 is OH; and R^{10} is SO_3Na (2-((4-oxo-3,5-dibromo-2,5-cyclohexadien-1-ylidene)(4-hydroxy-3,5-dibromophenyl)methyl)-3,4,5,6-tetrabromophenylsulfonic acid sodium salt or tetabromophenol blue sodium salt);

X is O; R^1 is CO_2Et; R^2-R^6, R^{10}, R^{13} and R^{14} are H; R^7, R^9, R^{11} and R^{12} are Br; and R^8 is OH (ethyl 2-((4-oxo-3,5-dibromo-2,5-cyclohexadien-1-ylidene)(4-hydroxy-3,5-dibromophenyl)methyl)benzoate or 3',3'',5',5''-tetrabromophenolphthalein ethyl ester);

X is O; R^1, R^5-R^9, R^{13} and R^{14} are H; R^2, R^4, R^{11} and R^{12} are Br; R^3 is OH; and R^{10} is SO_3Na (2-((4-oxo-3,5-dibromo-2,5-cyclohexadien-1-ylidene)(4-hydroxy-3,5-dibromophenyl)methyl)phenylsulfonic acid sodium salt or bromophenol blue sodium salt);

X forms propylenylammonium with R^{11} and R^{12}; R^1, R^6, R^7, R^9 and R^{14} are H; R^2 and R^4 form propylenylamino with R^3; R^5 and R^{13} form O; R^8 is SO_3H; and R^{10} is SO_3Na (2-(9a-aza-2,3,5,7,8,9-hexahydrobenzonaphtheno[5,4-e]-3a-aza-2,3,4,5,6-pentahydrobenzonaphtheno[9,8-b]-2H-pyran-4-yl)benzene-1,3-disulfonic acid monohydrate or sulforhodamine 101 hydrate);

X is (4-oxysulfonylphenylmethyl)(ethyl)ammonium; R^1, R^2, R^4, R^6, R^7 and R^9-R^{13} are H; R^3 is (4-SO_3Na-phenylmethyl)(ethyl)amino; R^5 and

R^{14} are methyl; and R^8 is 4-ethoxyphenylamino (4-((4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)imminium-2-methyl-2,5-cyclohexadien-1-ylidene)(2-methyl-4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)aminophenyl))methyl-N-(4-ethoxyphenyl)aniline sodium salt or brilliant blue G);

X is (4-oxysulfonylphenylmethyl)(ethyl)ammonium; R^1, R^2, R^4-R^7 and R^9-R^{14} are H; R^3 is (4-SO_3Na-phenylmethyl)(ethyl)amino; and R^8 is 4-ethoxyphenylamino (4-((4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)-imminium-2,5-cyclohexadien-1-ylidene)(2-methyl-4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)aminophenyl))methyl-N-(4-ethoxyphenyl)aniline sodium salt or coomassie brilliant blue R-250);

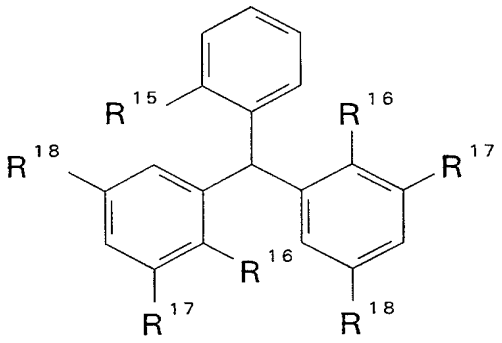
X is (4-oxysulfonylphenylmethyl)(ethyl)ammonium; R^1, R^2, R^4, R^6, R^9-R^{13} are H; R^3 is (4-SO_3Na-phenylmethyl)(ethyl)amino; R^5, R^7 and R^{14} are methyl; and R^8 is ethylamino (4-((4-(N-(4-hydroxysulfonylphenyl)methyl-N-ethyl)imminium-2-methyl-2,5-cyclohexadien-1-ylidene)(2-methyl-4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)aminophenyl))methyl-N-ethyl-2-methylaniline sodium salt or page blue G90);

X is O; R^1, R^6-R^9 and R^{13} are H; R^2 and R^{11} are Br; R^3 is OH; R^4 and R^{12} are isopropyl; R^5 and R^{14} are methyl; and R^{10} is SO_3Na (2-((4-oxo-3-bromo-5-isopropyl-2-methyl-2,5-cyclohexadien-1-ylidene)(3-bromo-4-hydroxy-5-isopropyl-2-methylphenyl)methyl)phenylsulfonic acid sodium salt or bromothymol blue sodium salt); and

X is NH; R^1, R^2, R^4-R^6 and R^9-R^{14} are H; R^3 and R^8 are amino; and R^7 is methyl (4-((4-aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl)-2-methylaniline hydrochloride or fuchsine).

ii. Compounds of formula (IIb)

Preferred compounds of formula (II) have formula (IIb):



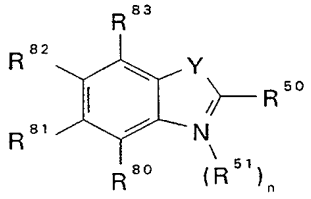
(IIb)

where R^{15} is methoxycarbonyl or hydroxysulfonyl; R^{16} is selected from hydrogen, ethoxy and methoxy; and R^{17} and R^{18} are each selected from hydrogen and Cl.

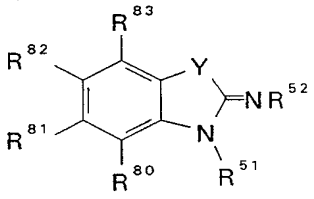
Presently preferred compounds of formula (IIb) include methyl 2-benzydrylbenzoate, α,α-bis(3,5-dichloro-2-ethoxyphenyl)-ortho-toluenesulfonic acid sodium salt and α,α-bis(3,5-dichloro-2-methoxyphenyl)-ortho-toluenesulfonic acid sodium salt.

b. Heteroaryl Compounds

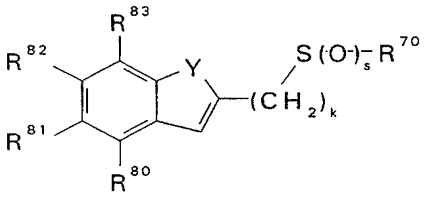
In another embodiment, the compounds of formula (I) are heteroaryl derivatives of formulae (III):



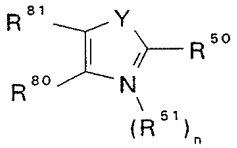
(IIIa)



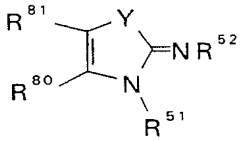
(IIIb)



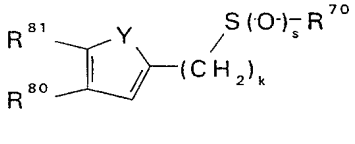
(IIIc)



(IIId)



(IIIe)



(IIIf)

and pharmaceutically acceptable derivatives thereof, where:

Y is O, S or NR^{40};

R^{50} is alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, (N-alkyl-, alkenyl-, hydroxyalkyl- or hydroxycarbonylalkyl-heteroarylium)alkyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$ or $NR^{40}R^{41}$;

R^{51} is selected from hydrogen, alkyl, alkenyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

n is 0 or 1;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is selected from aryl, heteroaryl and $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is aryl, heteroaryl or N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl or $S(O)_m$-aryl or -heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z, preferably from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene which are unsubstituted or substituted with 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i);

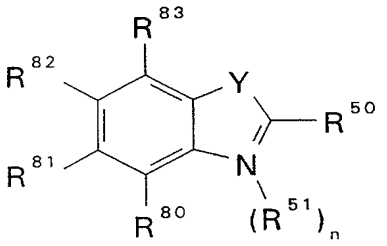
k is 0-6; and s is 0-2.

In embodiments where n is 1, the nitrogen atom of formulae (IIIa) and (IIId) is positively charged and the compounds are heteroarylium compounds, such as benzoxazolium, benzothiazolium and benzimidazolium compounds. In these embodiments, a counterion may be present, forming a salt with the positively-charged nitrogen of the heteroarylium group. Such counterions include, but are not limited to, halide, sulfate, tetrahaloborate and perchlorate.

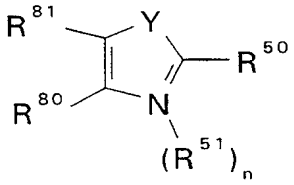
In embodiments where n is 0, R^{51} is absent from formulae (IIIa) and (IIId), and the nitrogen atom is neutral. In such embodiments, the compounds are heteroaryl compounds, such as benzoxazoles, benzothiazoles and benzimidazoles.

i. Compounds of formulae (IIIa) and (IIId)

In a preferred embodiment, the compounds of formula (I) are of formula (IIIa) or (IIId):



(IIIa)



(IIId)

where:

Y is O, S or NR^{40};

R^{50} is alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, (N-alkyl-, alkenyl-, hydroxyalkyl- or hydroxycarbonylalkyl-heteroarylium)alkyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$ or $NR^{40}R^{41}$;

R^{51} is selected from hydrogen, alkyl, alkenyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl, heteroaralkyl, aryl and heteroaryl, preferably from alkyl, alkenyl, hydroxycarbonylalkyl and hydroxyalkyl;

n is 0 or 1;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is aryl, heteroaryl or N=heterocyclyl; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z, preferably from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i).

In more preferred embodiments, the compounds have formulae (IIIa) or (IIId) where:

Y is O, S or ethylamino;

R^{50} is selected from 3-(N-propyl-2-benzothiazolium)prop-1-yl, 3-(N-(2-hydroxy-1-ethyl)-2-benzothiazolium)prop-1-yl, 3-(N-(2-propen-1-yl)-2-benzothiazolium)prop-1-yl, 3-(N-(3-hydroxycarbonyl-1-propyl)-2-benzothiazolium)prop-1-yl, 2-(4-dimethylaminophenyl)ethenyl, 3-(N-ocatadecylbenzoxazol-2-inylidene)propenyl, 2-ethyl-3-(N-ethylnaphthothiazol-2-inylidene)propenyl, 2-(N-acetyl-N-phenylamino)ethenyl, (N-methylbenzothiazolin-2-ylidene)aminoazo, 2-(5-(2-(5-chloro-N-ethylbenzothiazolin-2-ylidene)ethylidenyl)-1-diphenylamino-1-cyclopenten-2-yl)ethenyl, 2-hydroxypropenyl, 4-dimethylaminophenyl, 2-methyl-3-(N-ethylnaphthothiazol-2-inylidene)propenyl, (N,N'-dimethylbenzimidazolin-2-ylidene)aminoazo, 3-(N,N'-diethyl-5-cyanobenzimidazolin-2-ylidene)propenyl, 3-ethoxy-1H-phenalen-1-ylidenemethyl, 3-(N-ethylbenzothiazolin-2-ylidene)-2-methylpropenyl, 3-(N-ethylbenzothiazolin-2-ylidene)propenyl, 5-(N-ethylbenzothiazolin-2-ylidene)pentadienyl, 2-amino-1-naphthylazo, 4-phenylaminophenylazo, pentamethylphenylmethylthio, 4-(bis(2-hydroxyethyl)amino)phenylazo, phenylmethoxy, 4-(3-(4-(N-benzothiazol-2-yl)piperidinyl)propyl)piperidinyl, 2-(4-methylphenylsulfonyl)aminophenyl, benzothiazol-2-yldithio, 3-(N-(2-preopeny-1-yl)benzothiazolin-2-ylindene)propenyl, 5-(N-propylbenzothiazolin-2-ylidene)pentadienyl and 6-amino-1,4-dihydro-3-cyano-4-(4-cyanophenyl)-benzothiazolin[2,3-a]pyridin-5-yl;

R^{51} is methyl, ethyl, propyl, 2-propen-1-yl, 2-hydroxy-1-ethyl, octadecyl or 3-hydroxycarbonyl-1-propyl;

n is 0 or 1; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from hydrogen, methyl, methoxy and Cl; or

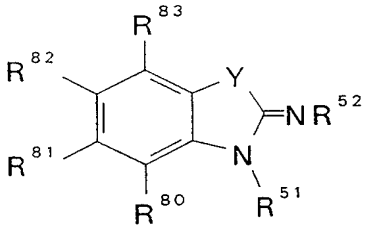
(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene and the others are selected as in (i).

Among the presently preferred compounds of formulae (IIIa) and (IIId) are N-ethyl-2-(2-(4-dimethylaminophenyl)ethenyl)naphtho[2,1-d]thiazolium iodide, 3,3'-dioctadecyloxacarbocyanine perchlorate, N-ethyl-2-(2-ethyl-3-(N-ethylnaphtho[1,2-d]thiazolidin-2-ylidene)propenyl)naphtho[1,2-d]thiazolium bromide, N,N'-dioctadecyloxacarbocyanine para-toluenesulfonate, 2-(2-acetanilinovinyl)-3-ethylbenzothiazolium iodide, 3-methyl-2-((3-methyl-2-benzothiazolinylidene)aminoazo)benzothiazolium tetrafluoroborate, 5-chloro-N-ethyl-2-(2-(5-(2-(5-chloro-N-ethylbenzothiazolin-2-ylidene)ethylidenyl)-1-diphenylamino-1-cyclopenten-2-yl)ethenyl)benzothiazolium perchlorate, N-ethyl-2-(2-hydroxypropen-1-yl)benzothiazolium chloride, 3,6-dimethyl-2-(4-dimethylaminophenyl)benzothiazolium bromide, N-ethyl-2-(2-methyl-3-(N-ethylnaphtho[1,2-d]thiazolidin-2-ylidene)propenyl)naphtho[1,2-d]thiazolium bromide, 2-(4-dimethylamino)-styryl)-3-ethylbenzothiazolium iodide, N-methyl-2-((N,N'-dimethylbenzimidazolin-2-ylidene)aminoazo)benzothiazolium perchlorate, 1-ethyl-2-(3-(N,N'-diethyl-5-cyanobenzimidazolin-2-ylidene)propenyl)-3-(4-hydroxysulfonyl-1-butyl)benzimidazole, 2-(3-ethoxy-1H-phenalen-1-ylidenemethyl)-3-ethylbenzothiazolium tetrafluoroborate, 3,3'-diethyl-9-methylthiacarbocyanine iodide, 3,3'-diethylthiacarbocyanine iodide, 3,3'-diethylthiadicarbocyanine iodide, 3-methyl-2-bromothiazolinone (1,2-dihydro-2-imino-1-naphthylidene)hydrazone hydroiodide, 2-(4-phenylaminophenylazo)-N-methylbenzothiazolium iodide, 2-(pentamethylphenyl)methylthiobenzothiazole, 2-(4-(bis(2-hydroxyethyl)amino)phenylazo)-7-methoxybenzothiazole, 2-

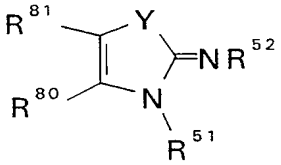
phenylmethoxybenzothiazole, 2-(4-(3-(4-(N-benzothiazol-2-yl)piperidinyl)propyl)piperidinyl)benzothiazole, 2-(2-(4-methylphenyl-sulfonyl)aminophenyl)naphtho[2,3-d]oxazole, bis(2-benzothiazolyl) disulfide, 3,3'-di(2-propen-1-yl)thiacarbocyanine iodide, 3,3'-dipropylthiadicarbocyanine iodide and 2-(6-amino-1,4-dihydro-3-cyano-4-(4-cyanophenyl)-benzothiazolin[2,3-a]pyridin-5-yl)benzothiazole.

ii. Compounds of formulae (IIIb) and (IIIe)

In a preferred embodiment, the compounds of formula (I) are of formulae (IIIb) and (IIIe):



(IIIb)



(IIIe)

where:

Y is O, S or NR^{40};

R^{51} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

R^{52} is selected from aryl, heteroaryl and $NR^{60}R^{61}$;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl or $S(O)_m$-aryl or -heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z, preferably from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

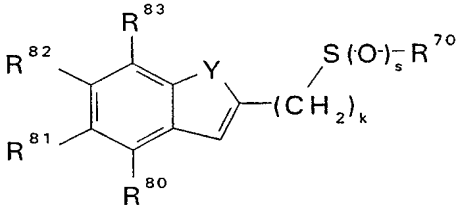
(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i).

In more preferred embodiments, the compounds are of formulae (IIIb) or (IIIe) where Y is S; R^{51} is methyl or ethyl; R^{52} is (4-nitrophenylazo)(phenyl)methylimino, 2-imino-5,6-benzo-3-cyclohexen-1-ylimino, 4-dimethylaminophenyl, 3,4-propylenylphenylmethylimino, 1-(3-aminophenyl)ethylimino, 4-dimethylaminophenylmethylimino or 2-nitrophenylsulfonylamino; and R^{80}, R^{81}, R^{82} and R^{83} are all hydrogen.

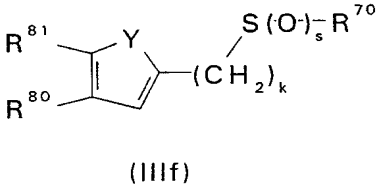
Presently most preferred compounds of formulae (IIIb) and (IIIe) include 4-nitrophenylazobenzoyl N-methylbenzothiazolidinone hydrazine bishydrazone, 2-imino-5,6-benzo-3-cyclohexenone N-methylbenzothiazolidinone hydrazine bishydrazone, N-ethylbenzothiazolidinone 4-dimethylaminophenylimine, 3,4-propylenylbenzaldehyde N-methylbenzothiazolidinone hydrazine bishydrazone, 3-aminoacetophenone N-methylbenzothiazolidinone hydrazine bishydrazone, 4-dimethylaminobenzaldehyde N-methylbenzothiazolidinone hydrazine bishydrazone or N-methylbenzothiazolidinone 2-nitrophenylsulfonylhydrazone.

iii. Compounds of formulae (IIIc) and (IIIf)

In a preferred embodiment, the compounds of formula (I) are of formulae (IIIc) and (IIIf):



(IIIc)



(IIIf)

where:

Y is O, S or NR^{40}, preferably O or S;

R^{70} is alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, preferably aryl or heteroaryl;

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z, preferably from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i);

k is 0-6; and s is 0-2.

In more preferred embodiments, k is 1 and s is 0 or 2.

In particularly preferred embodiments, the compounds have formulae (IIIc) and (IIIf) where Y is O; R^{70} is aryl; R^{80}, R^{81}, R^{82} and R^{83} are all halide or pseudohalide; k is 1 and s is 0 or 2. More preferably, Y is O, R^{70} is selected from 3-trifluoromethylphenyl, 4-chlorophenyl and 4-methoxyphenyl; R^{80}, R^{81}, R^{82} and R^{83} are all fluoro; k is 1 and s is 0 or 2.

Presently most preferred compounds of formulae (IIIc) and (IIIf) are 2-(3-trifluoromethylphenylthiomethyl)-4,5,6,7-tetrafluorobenz[d]oxazole, 2-(4-chlorophenylsulfonylmethyl)-4,5,6,7-tetrafluorobenz[d]oxazole and 2-(4-methoxyphenylthiomethyl)-4,5,6,7-tetrafluorobenz[d]oxazole.

c. Aryl and heteroaryl Derivatives

Also of interest for use in the compositions and methods are any pharmaceutically-acceptable derivatives, including salts, esters, acids, bases, solvates, hydrates and prodrugs of the aryl and heteroaryl compounds. Such derivatives may be readily prepared by methods known to those of ordinary skill in the art. Pharmaceutically-acceptable salts, include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-

methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

2. Formulations for oral administration

Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

In certain embodiments, the formulations are solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example,

lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as sodium cyclamate and saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of

sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. For example, if the compound is used for treating asthma or hypertension, it may be used with other bronchodilators and antihypertensive agents, respectively. The active ingredient is a compound or pharmaceutically acceptable derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring
agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substance used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic adds and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial

sweetening agents such as sodium cyclamate and saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic adds include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Patent Nos 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, e.g., in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be easily measured for administration.

Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (e.g., propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. Re 28,819 and 4,358,603.

In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

3. Injectables, solutions and emulsions

Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, e.g., U.S. Patent No. 3,710,795) is also contemplated herein. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

Parenteral administration of the formulations includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as the lyophilized powders described herein, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (Tween® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

The unit-dose parenteral preparations are packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

4. Topical administration

Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

The compounds or pharmaceutically acceptable derivatives thereof may be formulated as aerosols for topical application, such as by inhalation (see, e.g., U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically diameters of less than 50 microns, preferably less than 10 microns.

The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical

administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

5. Compositions for ophthalmic administration

For ophthalmic indications, the compositions are formulated in an ophthalmically acceptable carrier. For the ophthalmic uses herein, local administration, either by topical administration or by injection is preferred. Time release formulations are also desirable. Typically, the compositions are formulated for single dosage administration, so that a single dose administers an effective amount.

Ophthalmologically effective concentrations or amounts of one or more of the compounds are mixed with a suitable pharmaceutical carrier or vehicle. The concentrations or amounts of the conjugates that are effective requires delivery of an amount, upon administration, that prevents or substantially reduces the effects of FGF-mediated ophthalmological conditions, including, but not limited to, diabetic retinopathy, corneal clouding following excimer laser surgery, closure of trabeculectomies, hyperproliferation of lens epithelial cells following cataract surgery and the recurrence of pterygii.

The compounds can also be mixed with other active materials, that do not impair the desired action, or with materials that supplement the desired action, including viscoelastic materials, such as hyaluronic acid, which is sold under the trademark HEALON (solution of a high molecular weight (MW of about 3 million) fraction of sodium hyaluronate; manufactured by Pharmacia, Inc. see, e.g., U.S. Patent Nos.

5,292,362, 5,282,851, 5,273,056, 5,229,127, 4,517,295 and 4,328,803), VISCOAT (fluorine-containing (meth)acrylates, such as, 1H,1H,2H,2H-heptadecafluorodecylmethacrylate; see, e.g., U.S. Patent Nos. 5,278,126, 5,273,751 and 5,214,080; commercially available from Alcon Surgical, Inc.), ORCOLON (see, e.g., U.S. Patent Nos. 5,273,056; commercially available from Optical Radiation Corporation), methylcellulose, methyl hyaluronate, polyacrylamide and polymethacrylamide (see, e.g., U.S. Patent No. 5,273,751). The viscoelastic materials are present generally in amounts ranging from about 0.5 to 5.0%, preferably 1 to 3% by weight of the conjugate material and serve to coat and protect the treated tissues. The compositions may also include a dye, such as methylene blue or other inert dye, so that the composition can be seen when injected into the eye or contacted with the surgical site during surgery.

6. Formulations for other routes of administration

Depending upon the condition treated other routes of administration, such as topical application, transdermal patches, an rectal administration are also contemplated herein.

For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax, (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include

spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 g.

Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

7. Articles of manufacture

The compositions containing compounds or pharmaceutically acceptable derivatives may be packaged as articles of manufacture containing packaging material, a composition containing a compound or pharmaceutically acceptable derivative thereof provided herein, which is effective for antagonizing the effects of an FGF peptide, preferably bFGF, ameliorating the symptoms of an FGF-mediated disorder, or inhibiting binding of an FGF peptide to an FGF receptor with an IC_{50} of less than about 500 μM, within the packaging material, and a label that indicates that the composition containing the compound or derivative thereof is used for antagonizing the effects of FGF, treating FGF-mediated disorders or inhibiting the binding of an FGF peptide to an FGF receptor.

E. Methods of treating of FGF-mediated disorders

Methods using the compositions containing therapeutically effective concentrations of the compounds of formula (I) or pharmaceutically acceptable derivatives thereof are also provided. The compositions containing such compounds are used for treating FGF-mediated disorders, particularly proliferative disorders, in which FGF causes or contributes to the pathology. In particular, methods for using the compositions to prevent the undesired growth and proliferation of FGF-sensitive cells occurring in vascular disorders characterized by accelerated smooth muscle cell proliferation, such as rheumatoid arthritis, tumor angiogenesis, Kaposi's sarcoma, restenosis, In-Stent

restenosis, certain ophthalmic disorders and dermatological disorders, such as psoriasis, are provided herein.

Preferably, the medicament containing the compound is administered intravenously (IV), although treatment by localized administration may be tolerated in some instances. Generally, the medicament containing the compound is injected into the circulatory system of a subject in order to deliver a dose to the targeted cells. Targeting may be effected by linking the compound to a targeting agent specific for FGF receptors, particularly bFGF receptors. Dosages may be determined empirically, but will typically be in the range of about 0.01 mg to about 100 mg of the compound per kilogram of body weight as a daily dosage.

Restenosis and vascular injury

Methods for treating vascular injury, particularly, restenosis or In-Stent restenosis by contacting the vascular wall with an effective amount of a composition containing compound(s) of formulae (I), (II) or (III) are provided (see generally, Lindner *et al.* Proc. Natl. Acad. Sci. USA **1991**, 88, 3739; Kearney *et al.* Circulation **1997**, 95, 1998).

Atherosclerosis, also referred to as arteriosclerosis, results from the development of an intimal lesion and the subsequent narrowing of the vessel lumen. Frequently, atherosclerosis originally appears as a result of the buildup of plaque which lines the interior of blood vessels, particularly the arteries. Whereas bypass surgery is sometimes employed to replace such clogged arteries, in recent years, a number of surgical procedures have been developed so as to interarterially remove such plaque, often by balloon catheterization or other such treatments in which the plaque is either compressed against or scraped away from the interior surface of the artery. This scraping of the interior wall removes endothelial cells, which constitute the lining of the blood vessel. As a

result of this removal, the smooth muscle cells (SMCs), which are normally located exterior of the endothelial cells (ECs) and form the blood vessel structure, begin to grow and multiply causing a narrowing of the vessel lumem. Not infrequently, the patient so treated finds a recurrence of such narrowing of the vessel lumen in a relatively short period thereafter as a result of this proliferation, generally referred to as restenosis, requiring a repetition of the surgical procedure to again remove the increasing blockage.

Proliferating SMCs express functional FGF receptors and are responsive to bFGF. By inhibiting proliferation of migrating smooth muscle cells (SMCs), it is possible to prevent the undesirable growth and ultimate clogging which occurs following vascular injury, and which is generally referred to as restenosis. Basic FGF appears to play a pivotal role in the subsequent responses of the vascular wall. Basic FGF is known to be synthesized by endothelial and smooth muscle cells (SMCs) and is thought to be stored in the subendothelial matrix, and in some instances, this growth factor is released from cells after injury. Therefore, compounds that inhibit FGF-mediated proliferation of SMCs may be used in methods for treating restenosis by preventing the proliferation that causes the narrowing of the vessel lumem.

Treatment is effected by administering a therapeutically effective amount of a medicament containing the compound in a physiologically acceptable carrier or recipient, in a manner so that the compound reaches regions in a human or other mammal where the compound will inhibit the proliferation of the target cells. For restenosis, intraarterial infusion will be among the preferred methods. Although a single dose should inhibit neointimal proliferation, IV administration over a period of time is preferred.

The compounds for treating restenosis may be formulated for intravenous or local administration. Alternatively, compounds may be conjugated to an agent that specifically targets proliferating SMCs, such as antibodies, hormones, ligands or the like to improve delivery and uptake of the compound. The therapeutically effective concentration may be determined empirically by testing the compounds in known in vitro and in vivo systems (see, e.g., Moscatelli *et al.* J. Cell. Physiol. **1987**, 131, 123-130); mitogenic assays (Gospardarowicz *et al.* Proc. Natl. Acad. Sci. U.S.A. **1984**, 81, 6963-6967; Thomas *et al.* Proc. Natl. Acad. Sci. U.S.A. **1984**, 81, 357); stimulation of angiogenesis in vitro (see, e.g., European Patent Application No. EP 645 451); cell proliferation assays or heparin binding assays (see, e.g., International Application Publication No. WO 92/12245); assays measuring the release of cellular proteases (Moscatelli *et al.* Proc. Natl. Acad. Sci. U.S.A. **1986**, 83, 2091-2095; Phadke Biochem. Biophys. Res. Comm. **1987**, 142, 448-453); and, assays for the promotion of FGF-mediated neurite outgrowth and neuron survival (Togari *et al.* Biochem. Biophys. Res. Comm. **1983**, 114:1189-1193; Wagner *et al.* J. Cell Biol. **1986**, 103, 1363-1367) and then extrapolated therefrom for dosages for humans.

Rheumatoid arthritis

Rheumatoid arthritis is a systemic, chronic inflammatory disease, that is characterized by the destruction of the joint cartilage and inflammation of the synovium. The hallmark feature of rheumatoid arthritis is the production circulating autoantibodies, also referred to as rheumatoid factors, which are reactive with the Fc portions of the patients own IgG molecules (e.g., see Abbas *et al.*, Cellular and Molecular Immunology, W.B. Saunders Co., Philadelphia, PA).

One of the systemic complications of rheumatoid arthritis is the formation of injurious immune complexes in the synovial fluid of the joints that initiates vascular inflammation by activation of the complement cascade. T-cells, activated B-cells, plasma cells and macrophages are often found in synovial fluid of affected joints as well as a variety of soluble proteins, such as cytokines (e.g., interleukin-1, IFN-γ and tumor necrosis factor (TNF)) and growth factors, such as bFGF. It has been suggested that cytokines act in concert with the inflammatory mediators, e.g., bFGF, to cause local tissue destruction. Chronically, cytokines and bFGF stimulate fibroblast and epithelial proliferation resulting in angiogenesis, and prolonged exposure can result in hyperproliferation of epithelial cells that form fibrous tissue, referred to as fibrosis.

Thus, compounds that inhibit the FGF-mediated hyperproliferation of epithelial cells may be used to treat rheumatoid arthritis. The compounds for treating rheumatoid arthritis may be formulated for oral administration or intravenous injection and an effective concentration may be administered. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

Tumor Angiogenesis

Angiogenesis plays a critical role in embryonic development and in several physiologic and pathologic conditions, including wound healing, ovulation, diabetic retinopathy and malignancy. In particular, without the nutrients and oxygen provided via this neovascularization, solid tumors would be unable to grow beyond about 2 mm in diameter.

Evidence exists that several cancers, including melanomas, ovarian, pancreatic and some colon carcinomas, have receptors for bFGF. Testing with radioactive binding assays on a number of human

carcinogenic cell lines isolated from human cancers demonstrated that many but not all of these cell lines bind ^{125}I-FGF. Thus, compounds that inhibit the activity of FGF may be used to treat tumorigenic pathophysiological conditions caused by a proliferation of cells which are sensitive to FGF mitogenic stimulation. In addition, tumor growth can be inhibited by modulating FGF receptor activity in the components of blood vessels (e.g., vascular endothelial cells or vascular SMCs) (Haberman Angiogenesis **1996**, 98-1 to 98-20; Colville-Nash *et al.* Molec. Med. Today **1997**, 14; Shawver *et al.* Drug Discovery Today **1997**, 2, 50).

The compounds may be specifically targeted to tumorigenic tissues by linking the compound to an agent that specifically binds to the surface of the tumorigenic cell, e.g., an anti-tumor antigen antibody, or linking the compound to an agent that is preferentially interacts with or taken up by targeted tumor. In addition, compounds may be encapsulated in tissue-targeted liposomal suspensions for targeted delivery of the compound.

The compounds for treating tumor angiogenesis may be formulated for topical application and administered to the skin, e.g., for treatment of melanoma, or may be formulated for intravenous administration for treatment of solid tumors, such as carcinomas. The therapeutically effective concentration may be determined empirically by testing the compounds in known in vitro (e.g., inhibition of angiogenesis in vitro (see, e.g., European Patent Application No. EP 645 451)) and then extrapolated therefrom for dosages for humans.

Ophthalmic Disorders

Pharmaceutical compositions provided herein may be used in methods of treating ophthalmic disorders resulting from FGF-mediated hyper-proliferation of lens epithelial cells, fibroblasts or keratinocytes. In particular, ophthalmic disorders that may be treated using the methods

and compositions provided herein include, but are not limited to, corneal clouding following excimer laser surgery, closure of trabeculectomies, hyperproliferation of lens epithelial cells following cataract surgery, the recurrence of pterygii and diabetic retinopathy (see, Dell Drug Discovery Today **1996**, 1, 221).

The compounds for treating ophthalmic disorders may be formulated for local or topical application and administered by topical application of an effective concentration to the skin and mucous membranes, such as in the eye. The compositions may also include a dye, such as methylene blue or other inert dye, so that the composition can be seen when injected into the eye or contacted with the surgical site during surgery. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

The ophthalmologic indications herein are typically treated locally either by the application of drops to the affected tissue(s), contacting with a biocompatible sponge that has absorbed a solution of the conjugates or by injection of a composition. For the indications herein, the composition will be applied during or immediately after surgery in order to prevent closure of the trabeculectomy, prevent a proliferation of keratocytes following excimer laser surgery, prevent the proliferation of lens epithelial cells following cataract surgery or to prevent a recurrence of pterygii. The composition may also be injected into the affected tissue following surgery and applied in drops following surgery until healing is completed. For example, to administer the formulations to the eye, it can be slowly injected into the bulbar conjunctiva of the eye.

The following example is included for illustrative purposes only and ia not intended to limit the scope of the invention.

EXAMPLE 1

Assays for identifying compounds that exhibit FGF antagonistic activity

A. Soluble FGF receptor assay

Compounds of formulae (I) that exhibit FGF antagonist activity were and can be identified by testing their ability to compete with ^{125}I-bFGF for binding to one or more FGF receptor or FGF-binding fragment thereof. These compounds have been tested in a binding assay that uses a recombinant FGF receptor fusion protein in which the extracellular domain of a human FGF receptor, FGFR1, was fused to the amino terminal fragment of tissue plasminogen activator (tPA) protein. This fusion protein retains the ability to bind FGF, such as bFGF (Zhu *et al.* J. Biol. Chem. **1995**, 270, 21869-21874).

(i) Isolation of DNA encoding the shorter form of human fibroblast growth factor receptor 1 (FGFR1)

The nucleotide sequence of the DNA encoding the shorter form of human basic fibroblast growth factor receptor 1 (FGFR1) has been determined (e.g., Itoh *et al.* Biochem. Biophys. Res. Comm. **1990**, 169:680-685). This shorter form of FGFR1 is a 731 amino acid polypeptide that has a signal peptide, two extracellular immunoglobulin-like domains, a transmembrane domain and an intracellular tyrosine kinase domain.

Based on the reported sequence, two oligonucleotides complementary to sequences flanking the FGFR1 coding region were synthesized and used as primers in polymerase chain reactions (PCR) to isolate a DNA encoding a full-length human FGFR1 from a human aorta cDNA library (Quickclone, Clontech, Palo Alto, CA). PCR amplification was performed using a commercially available PCR kit according to manufacturer's instructions (Perkin Elmer Cetus, Norwalk, CT). An oligonucleotide corresponding to nt -20 to +5, relative to the A of the

ATG initiation codon of FGFR1, (e.g., Itoh *et al.* Biochem. Biophys. Res. Comm. **1990**, 169, 680-685) and an oligonucleotide complementary to nt 2218-2243 were used as primers to amplify a 2,243 bp PCR product encoding the entire FGRF1 coding region.

The full-length FGFR1-encoding DNA was used as a template for a subsequent PCR reaction, performed as described above, to amplify a 869 bp DNA fragment encoding only the FGFR1 extracellular domain. Simultaneously, a HindIII restriction endonuclease site was introduced upstream of the FGFR1 initiation codon and a SalI site was introduced downstream of the second immunoglobulin-like extracellular domain (IgII) to facilitate cloning of the amplified product.

The HindIII site was introduced at nt -8 to -3 during the PCR reaction by synthesizing an oligonucleotide primer corresponding to nt -12 to +22 that introduced nucleotide changes at three positions in the FGFR1 sequence: nt -3 (G to T), nt -6 (A to G) and nt -8 (G to A). The SalI site was introduced at nt 849 to nt 854 by synthesizing an oligonucleotide primer complementary to nt 823 to 857 containing nucleotide substitutions at three positions in the FGFR1 sequence: nt 849 (C to G), nt 851 (G to C) and nt 854 (G to C). The 857 bp PCR fragment was incubated with HindIII and SalI and purified by agarose gel electrophoresis according to the standard procedures (Sambrook *et al.* (1989) Molecular Cloning, 2nd ed., Cold Spring Harbor Laboratory Press, New York). The DNA was isolated from gel by electroelution and recovered by precipitation with ethanol.

Thus, the resulting HindIII to SalI DNA fragment consists of nt -7 to nt 849 of the FGFR1 cDNA described by Itoh *et al.* and encodes amino acid residues 1 to 284 of the shorter form of the bFGF receptor.

(ii) Isolation of DNA encoding human tissue plasminogen activator

The nucleotide sequence of the DNA encoding human tissue plasminogen activator (tPA) has been determined (e.g., see Pennica *et al.* Nature **1983**, 301, 214-221). Human tPA is a 562 amino acid polypeptide which is processed during secretion to its mature form by cleavage of a 35 amino acid signal peptide. Several regions of the primary structure of mature tPA have a high degree of homology to known structural domains of other proteins, such as homology to the finger and growth factor domains, the Kringle 1 and Kringle 2 domains of plasminogen and prothrombin and the C-terminal serine protease domain (e.g., see Ny *et al.* Proc. Natl. Acad. Sci. USA **1984**, 81, 5355).

Based on the reported sequence, oligonucleotides complementary to sequences flanking the tPA coding region were synthesized and used as primers in PCR reactions to isolate a full-length cDNA encoding human tPA from a human placenta cDNA library (Clontech, Palo Alto, CA). An oligonucleotide corresponding to nt -6 to +21, relative to the A of the initiation codon of the of human tPA prepro polypeptide (e.g., see Pennica *et al.* Nature **1983**, 301, 214-221) and an oligonucleotide complementary to nt 1558 to nt 1584 were used to amplify a 1591 bp DNA encoding the entire human tPA prepro polypeptide.

The full-length DNA was used as a template for a subsequent PCR reaction to amplify a 599 bp DNA encoding the a portion of the signal peptide-finger-growth factor-first Kringle domains of tPA, and which also to introduce an in-frame amber stop codon (i.e., UGA) at amino acid codon 180 of mature tPA sequence. Concurrently, a SalI restriction endonuclease site and a mutation substituting a Pro for an Arg at position -6 were introduced upstream of the first Ser codon of mature tPA and a BamHI site was introduced downstream of newly introduced

translational stop codon to allow for convenient subcloning of the amplified product. The substitution of Pro for Arg at amino acid residue position -6 introduces a proteolytic cleavage site for thrombin in the linker sequence (i.e., Phe-Pro-Arg-Gly at positions -7 to -4).

The SalI site and the amino acid substitution were introduced at nt 76 to 81 and 91 and 92 (nt -30 to -25 and -15 and -14, respectively, relative to the first nucleotide of mature tPA) during the PCR reaction by synthesizing an oligonucleotide primer corresponding to nt 72 to nt 111 containing nucleotide substitutions at six positions in the tPA sequence: nt 76 (A to G), nt 79 (C to G), nt 81 (T to C), nt 91 (A to C) and nt 92 (G to C). The BamHI site at nt 652 to nt 657 and translational stop codon at amino acid codon 180 (nt 642-644) were introduced by synthesizing an oligonucleotide primer complementary to nt 623 to 661 containing nucleotide substitutions at three positions in the tPA sequence: nt 644 (C to A), nt 655 (A to T) and nt 657 (G to C).

The amplified PCR fragment was incubated with SalI and BamHI and subjected to agarose gel electrophoresis according to the standard procedures (Sambrook *et al.* (1989) Molecular Cloning, 2nd ed., Cold Spring Harbor Laboratory Press, New York). The 585 bp DNA was isolated from gel by electroelution and recovered by precipitation with ethanol.

(iii) Construction of a vector for expressing human FGFR1-tPA fusion protein

The isolated SalI to BamHI fragment encoding the portion of human tPA was ligated into the SalI and BamHI sites of pUC18 to generate plasmid HTPA3/4-pUC18. HTPA3/4-pUC18 was then digested with HindIII and SalI into which the isolated HindIII to SalI FGFR1-encoding fragment was inserted. The plasmid carrying the FGFR1-tPA chimeric DNA was digested with HindIII and BamHI, subjected to agarose

gel electrophoresis and the 1,426 bp DNA fragment was excised from the gel and isolated as described above. The resulting DNA encodes a 472 amino acid peptide comprised of amino acids 1-284 of human FGFR1, a 10 amino acid linker sequence VDARFPRGAR, derived from the human tPA signal peptide, and amino acids 1-178 from human tPA. The resulting DNA encoding the FGFR1-tPA fusion protein is shown in SEQ ID No: 1 and the deduced amino acid is shown in SEQ ID No: 2.

The DNA of SEQ ID No. 1 was digested with HindIII to BamHI and the 1,434 bp fragment (nt 2-1435 of SEQ ID No: 1) was isolated and ligated into the mammalian expression vector pK4K for recombinant expression of the FGFR1-tPA fusion protein (Niidome *et al.* Biochem. Biophys. Res. Commun. **1994**, 203, 1821-1827). The plasmid pK4K is a pBR322-based vector that has unique HindIII and BamHI sites for directional cloning of heterologous DNAs whose expression is under the control of the SV40 early promoter. This plasmid also contains the β-lactamase and DHFR genes for use as selectable markers in prokaryotes and eukaryotic organisms, respectively.

(iv) Expression of FGFR1-tPA chimeric protein in mammalian cells

Baby hamster kidney cells (BHK cells; Waechter, D.E., *et al.* Proc. Natl. Acad. Sci., USA **1982**, 79, 1106) were transfected with 5 μg of the FGFR1-tPA-containing expression plasmid using the CellPhect calcium phosphate method according to manufacturer's instructions (Pharmacia, Sweden). Transfectants were selected for the presence of the DHFR gene by selecting resistance to methotrexate and maintained in Dulbecco's Eagle medium containing 10% fetal bovine serum and 250 nM methotrexate.

Upon expression, the recombinant FGFR1-tPA fusion protein is secreted into the surrounding culture medium. Recombinant FGFR1-tPA

fusion protein expression in BHK cells was monitored by sandwich enzyme-linked immunosorbent assays (sandwich ELISAs). A mouse IgG monoclonal antibody specific for human tPA, designated 14-6, was used as the capture antibody and a polyclonal, rabbit anti-IgG antibody conjugated to horseradish peroxidase was used as the secondary-labelled antibody.

(v) Purification of FGFR1-tPA chimeric protein

The recombinant FGFR1-tPA fusion protein was purified from conditioned medium of BHK-expressing cells by affinity chromatography. Transfected cells were grown as described above and the condition medium was harvested. The osmolarity of the conditioned medium was adjusted to a final concentration of 0.5 M NaCl by the addition of 5 M NaCl solution. The sample was applied onto a column of Cellulofine (Seikagaku Kogyo, Tokyo, Japan) conjugated with anti-tPA 14-6 monoclonal antibody previously equilibrated in column buffer (50 mM Tris-HCl, pH 7.5, and 0.5 M NaCl). The column was then washed with 10 column volumes of column buffer and bound fusion protein was eluted from the column by the addition of 0.2 M glycine-HCl, pH 2.5. Fractions (0.5 ml) were collected into a tube containing 0.5 ml of 1 M Tris-HCl, pH 8.0 to neutralize the acidic eluate. Eluted fractions were monitored for the presence of FGFR1-tPA protein by measuring the absorbance of each fraction at 280 nm. The FGFR1-tPA-containing fractions were dialyzed against PBS and concentrated to a final concentration of 1.5-2.0 mg/ml using Centriprep filters (AMICON).

(vi) Analysis of bFGF-FGFR1 interaction

The soluble, recombinant FGFR1-tPA fusion protein was immobilized to a solid support by attachment to the surface of the wells of an enzyme-linked immunosorbent assay plate (High binding plates, COSTAR). A 0.1 ml aliquot of a 10 μg/ml solution of rFGFR1-tPA in PBS

was added and the plate was incubated for approximately 16 hr at 4 °C. Unbound fusion protein was removed by washing three times with an equal volume of cold PBS.

To each well, a 0.1 ml aliquot of blocking buffer (25 mM HEPES, pH 7.5, 100 mM NaCl and 0.5% gelatin) was added, and the samples incubated for 1 hr at ambient temperature to prevent non-specific binding of reagents. The wells were washed three times with binding buffer (25 mM HEPES, pH 7.5, 100 mM NaCl and 0.3% gelatin) followed by addition of 0.1 ml of binding buffer supplemented with 2 μg/ml heparin and a range of 1-20 ng/ml of labelled ^{125}I-bFGF (800-1200 Ci/mmol; Amersham, Arlington Heights, IL) and incubated in the absence or presence of 2.5 μg/ml unlabelled bFGF or a test compound for 3 hr at ambient temperature. The buffer was removed by aspiration and the wells were washed twice each with PBS and a solution of 25 mM HEPES, pH 7.5, containing 2 M NaCl. Bound bFGF was dissociated from the immobilized fusion protein by the addition of two aliquots of a solution of 25 mM sodium acetate, pH 4.0, containing 2 M NaCl. The two sodium acetate washes were combined and the amount of radioactivity present was determined using a gamma counter.

The amount of bound radiolabelled bFGF in each well was calculated and the specificity of bFGF binding was analyzed according to Scatchard (Scatchard Ann. N.Y. Acad. Sci. **1949**, 51, 660). From this analysis, a 280 pM dissociation constant (K_D) for the binding of bFGF to the recombinant FGFR1-tPA fusion protein of was calculated. This value correlates well with 130 pM K_D value reported for bFGF binding to native FGFR1 receptors expressed in smooth muscle cells (Saltis *et al.* Arteriosclerosis **1995**, 118, 77-87).

B. Membrane-bound FGF receptor assays

(i) Competitive inhibition of FGF binding

The rabbit aortic smooth muscle cell line, Rb-1, expresses high and low affinity FGF receptors (e.g., see Nachtigal *et al.* In Vitro Cell. & Develop. Biol. 1989, 25, 892-897). Compounds of formula (I) that have FGF antagonist activity were and can be identified by their ability to compete with ^{125}I-bFGF for binding to the FGF receptors expressed on cell surface of such cells (see e.g., see, Moscatelli *et al.* J. Cell. Physiol. **1987**, 131, 123-130).

Rb-1 cells were grown in 24-well plates to near-confluence in Dulbecco's modified Eagle's medium (DMEM; GIBCO BRL) supplemented with 10% fetal bovine serum, penicillin (100 unit/ml) and streptomycin (100 μg/ml). The culture medium was removed by aspiration and the cells were incubated in binding buffer (serum-free DMEM supplemented with 20 mM HEPES (pH 7.5) and 0.1% BSA) containing 2.5 ng/ml recombinant human ^{125}I-bFGF (800-1200 Ci/mmol; Amersham, Arlington Heights, IL) and varying concentrations of test compound, for 2 hr at ambient temperature. The nonspecific binding of iodinated bFGF to Rb-1 cells was estimated in parallel reactions performed in the presence of an excess of unlabeled bFGF.

The cells were washed twice with cold phosphate-buffered saline (PBS) and the bFGF bound to low affinity heparan sulfate proteoglycan (HSPG) receptors was dissociated by the addition to each well of a 1 ml solution of 25 mM HEPES (pH 7.5) containing 2 M NaCl. Following removal of the low affinity sample, the bFGF bound to high affinity FGF receptors was dissociated by the addition to each well of a 1 ml solution of 25 mM sodium acetate (pH 4.0) containing 2 M NaCl. A 1 ml aliquot from each well was transferred to a polypropylene tube and the amount

of radioactivity present in the high affinity samples was determined using a gamma counter.

(ii) Competitive inhibition of EGF binding

The specificity of identified FGF antagonists was examined by measuring the ability of compounds to inhibit the binding of epidermal growth factor (EGF) to the surface of Rb-1 cells. Rb-1 cells were grown as described above and incubated in binding buffer containing 2 ng/ml of ^{125}I-EGF (>750 Ci/mmol; Amersham) under similar conditions. Non-specific binding of radiolabelled EGF was estimated in parallel reactions performed in an excess of unlabeled EGF.

After washing the cells twice with cold PBS, specifically bound EGF was dissociated from the cells by addition of a solution of 0.1% Triton-X-100 and 5 min incubation at ambient temperature. The amount of radioactivity in each supernatant was measured using a gamma counter.

C. Inhibition of ^{3}H-thymidine incorporation

The incorporation of radiolabelled nucleotides into newly synthesized cellular DNA may be used as an indicator of cell proliferation. SMCs, such as rabbit aortic SMCs, incorporate tritiated thymidine into DNA upon stimulation with bFGF or PDGF.

The effectiveness of compounds of formulae (I) as FGF antagonists was and can be assessed by measuring the inhibition of tritiated thymidine incorporation into the DNA of cultured SMCs incubated in the presence of bFGF, PDGF or EGF. An inoculum of approximately 2 X 10^4 rat aortic SMCs was added to a plurality of wells and the cells cultured for three days as described in EXAMPLE 1B(i). The cells were washed twice with serum-free medium (DMEM supplemented with 0.1 % BSA, 5 μg/ml transferrin, penicillin (100 unit/ml) and

streptomycin (100 ug/ml)) and cultured for an additional three days in serum-free DMEM medium.

After washing twice in serum-free DMEM medium, the follow was added to each well: 400 μl of serum-free DMEM, 50 μl of 3 ng/ml bFGF in DMEM and 50 μl of known concentration test compound in DMEM 1.0% DMSO for 23 hr at 37° C. To each well, 10μl of tritiated thymidine (^{3}H-thymidine, 50 μCi/ml) was added and cells were incubated for 1 hr (37 °C). The medium was removed and the cells were washed twice with cold PBS. An 500 μl aliquot of a cold 10% TCA solution was added to each well and the cells incubated at 4° C overnight. After washing three times in cold PBS, the cells were incubated in 500 μl of 0.5 N NaOH for 30 min and the pH of the sample was neutralized by the addition of an equal volume of 0.5 N HCl. The amount of radioactivity present the supernatant of each well was determined using a liquid scintillation counter.

D. Results

The percent inhibition of bFGF for each of the compounds described in detail above has been measured. Almost all of the compounds exhibited some inhibition of bFGF at concentrations of less than 500 μM. Many of the compounds exhibited some inhibition of bFGF at concentrations of less than 300 μM. Several of these compounds exhibited some inhibition of bFGF at concentrations of less than 30 μM, while a few had measured IC_{50} values of less than 15 μM.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition, comprising, in a pharmaceutically acceptable vehicle, a compound of formulae (I):

$$Ar^1\text{-}V^1 \quad \text{or} \quad Ar^2 = V^2 \qquad (I)$$

or a pharmaceutically acceptable derivative thereof, wherein:

Ar^1 is a monocyclic or fused bicyclic, tricyclic or tetracyclic aromatic or heteroaromatic group, wherein the heteroaromatic group contains one or two heteroatoms selected from O, S and N;

Ar^2 is a monocyclic or fused bicyclic, tricyclic or tetracyclic arylidene or heteroarylidene group, where the heteroarylidene group contains one or two heteroatoms selected from O, S, and N;

V^1 is selected from the group consisting of diarylalkyl, diheteroarylalkyl, alkenyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$, $NR^{40}R^{41}$ and $-(CH_2)_k-S(O)_s-R^{70}$, where k is 0-6 and s is 0-2;

V^2 is diarylalkylidene, diheteroarylalkylidene or $=NR^{52}$;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is aryl, heteroaryl or $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is selected from aryl, heteroaryl and N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

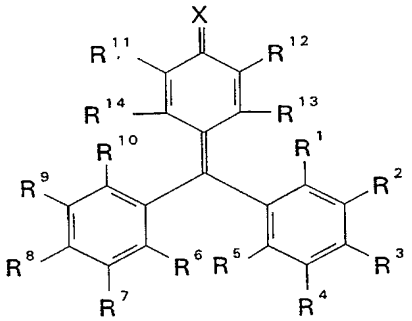
R^{70} is selected from alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

the aryl, heteroaryl, arylidene and heteroarylidene moieties of the compound of formula (I) are unsubstituted or are substituted with one or more substituents each independently selected from Z; and

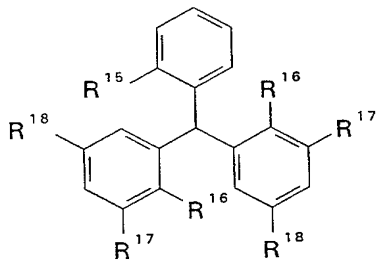
Z is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, hydroxysulfonyl, hydroxyphosphoryl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl, or any two Z groups substituting adjacent atoms may form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene,

wherein the compound modulates the interaction of an FGF peptide with an FGF receptor.

2. The pharmaceutical composition of claim 1, wherein the compound of formula (I) has formulae (II):



(IIa)



(IIb)

or a pharmaceutically acceptable derivative thereof, where:

R^1 and R^5 are each independently selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$, or, together with R^{13}, form oxy;

R^2 and R^4 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with R^3, form alkylenylamino;

R^3 is hydrogen, hydroxy, thioxy, alkoxy, aryloxy, SR^{40} or $NR^{40}R^{41}$, or, together with R^2 or R^4, forms alkylenylamino;

R^6 and R^{10} are each independently selected from hydrogen, halide, pseudohalide, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$;

R^7 and R^9 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^8 is hydrogen, halide, pseudohalide, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, aryloxy, heteroaryloxy, $NR^{40}R^{41}$, CO_2R^{20}, $PO_3(R^{20})_2$ or SO_nR^{20} where n is 0-3;

R^{11} is selected from hydrogen, halide and pseudohalide, or, together with X, forms alkylenylammonium;

R^{12} is hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with X, forms alkylenylammonium;

R^{13} is hydrogen, or, together with R^1 or R^5, forms oxy;

R^{14} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

X is oxy, thio, NR^{40} or $N^+R^{40}R^{41}$, or, together with R^{11} or R^{12}, forms alkylenylammonium;

R^{15} is CO_2R^{20}, SO_3R^{20} or $PO_3(R^{20})_2$;

R^{16} is selected from hydrogen, alkoxy, aralkoxy, heteroaralkoxy, aryloxy and heteroaryloxy;

R^{17} and R^{18} are each independently hydrogen, halide or pseudohalide;

R^{20} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl and Na; and

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene.

3. The pharmaceutical composition of claim 2, wherein the compound is of formula (IIa).

4. The pharmaceutical composition of claim 3, wherein:

R^1 and R^5 are each independently selected from hydrogen, methyl, CO_2Et and Br, or form oxy with R^{13};

R^2 and R^4 are each independently hydrogen, Br or isopropyl, or form propylenylamino with R^3;

R^3 is selected from hydrogen, hydroxy, amino, (4-hydroxysulfonyl-phenylmethyl)(ethyl)amino and (3-hydroxysulfonylphenylmethyl)(ethyl)-amino, or forms propylenylamino with R^2 or R^4;

R^6 and R^{10} are each independently hydrogen, Br or hydroxysulfonyl;

R^7 and R^9 are each independently selected from hydrogen, Br and methyl;

R^8 is hydrogen, hydroxy, Br, hydroxysulfonyl, ethylamino, amino or 4-ethoxyphenylamino;

R^{11} is hydrogen or Br, or forms propylenylammonium with X;

R^{12} is selected from hydrogen, Br and isopropyl, or forms propyleneylammonium with X;

R^{13} is hydrogen or forms oxy with R^1 or R^5;

R^{14} is selected from hydrogen and methyl; and

X is O, NH or (4-hydroxysulfonylphenylmethyl)(ethyl)imminium, or forms propylenylammonium with R^{11} and R^{12}.

5. The pharmaceutical composition of claim 3, wherein the compound is selected from the group consisting of 2-((4-oxo-3,5-dibromo-2,5-cyclohexadien-1-ylidene)(4-hydroxy-3,5-dibromophenyl)methyl)-3,4,5,6-tetrabromophenylsulfonic acid sodium

salt, ethyl 2-((4-oxo-3,5-dibromo-2,5-cyclohexadien-1-ylidene)(4-hydroxy-3,5-dibromophenyl)methyl)benzoate, 2-((4-oxo-3,5-dibromo-2,5-cyclohexadien-1-ylidene)(4-hydroxy-3,5-dibromophenyl)methyl)phenylsulfonic acid sodium salt, 2-(9a-aza-2,3,5,7,8,9-hexahydrobenzonaphtheno[5,4-e]-3a-aza-2,3,4,5,6-pentahydrobenzonaphtheno[9,8-b]-2H-pyran-4-yl)benzene-1,3-disulfonic acid monohydrate, 4-((4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)imminium-2-methyl-2,5-cyclohexadien-1-ylidene)(2-methyl-4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)aminophenyl))methyl-N-(4-ethoxyphenyl)aniline sodium salt, 4-((4-(N-(3-hydroxysulfonylphenyl)-methyl-N-ethyl)imminium-2,5-cyclohexadien-1-ylidene)(2-methyl-4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)aminophenyl))methyl-N-(4-ethoxyphenyl)aniline sodium salt, 4-((4-(N-(4-hydroxysulfonylphenyl)-methyl-N-ethyl)imminium-2-methyl-2,5-cyclohexadien-1-ylidene)(2-methyl-4-(N-(3-hydroxysulfonylphenyl)methyl-N-ethyl)aminophenyl))methyl-N-ethyl-2-methylaniline sodium salt, 2-((4-oxo-3-bromo-5-isopropoyl-2-methyl-2,5-cyclohexadien-1-ylidene)(3-bromo-4-hydroxy-5-isopropyl-2-methylphenyl)methyl)phenylsulfonic acid sodium salt and 4-((4-aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl)-2-methylaniline hydrochloride.

6. The pharmaceutical composition of claim 3, wherein the compound is selected from the group consisting of tetabromophenol blue sodium salt, 3',3'',5',5''-tetrabromophenolphthalein ethyl ester, bromophenol blue sodium salt, sulforhodamine 101 hydrate, brilliant blue G, coomassie brilliant blue R-250, page blue G90, bromothymol blue sodium salt and fuchsine.

7. The pharmaceutical composition of claim 3, wherein R^1-R^{14} and X are selected as in (i)-(ix) as follows:

(i) X is O; R^1, R^{13} and R^{14} are H; R^2, R^4-R^9, R^{11} and R^{12} are Br; R^3 is OH; and R^{10} is SO_3Na; or

(ii) X is O; R^1 is CO_2Et; R^2-R^6, R^{10}, R^{13} and R^{14} are H; R^7, R^9, R^{11} and R^{12} are Br; and R^8 is OH; or

(iii) X is O; R^1, R^5-R^9, R^{13} and R^{14} are H; R^2, R^4, R^{11} and R^{12} are Br; R^3 is OH; and R^{10} is SO_3Na; or

(iv) X forms propylenylammonium with R^{11} and R^{12}; R^1, R^6, R^7, R^9 and R^{14} are H; R^2 and R^4 form propylenylamino with R^3; R^5 and R^{13} form O; R^8 is SO_3H; and R^{10} is SO_3Na; or

(v) X is (4-oxysulfonylphenylmethyl)(ethyl)ammonium; R^1, R^2, R^4, R^6, R^7 and R^9-R^{13} are H; R^3 is (4-SO_3Na-phenylmethyl)(ethyl)amino; R^5 and R^{14} are methyl; and R^8 is 4-ethoxyphenylamino; or

(vi) X is (4-oxysulfonylphenylmethyl)(ethyl)ammonium; R^1, R^2, R^4-R^7 and R^9-R^{14} are H; R^3 is (4-SO_3Na-phenylmethyl)(ethyl)amino; and R^8 is 4-ethoxyphenylamino; or

(vii) X is (4-oxysulfonylphenylmethyl)(ethyl)ammonium; R^1, R^2, R^4, R^6, R^9-R^{13} are H; R^3 is (4-SO_3Na-phenylmethyl)(ethyl)amino; R^5, R^7 and R^{14} are methyl; and R^8 is ethylamino; or

(viii) X is O; R^1, R^6-R^9 and R^{13} are H; R^2 and R^{11} are Br; R^3 is OH; R^4 and R^{12} are isopropyl; R^5 and R^{14} are methyl; and R^{10} is SO_3Na; or

(ix) X is NH; R^1, R^2, R^4-R^6 and R^9-R^{14} are H; R^3 and R^8 are amino; and R^7 is methyl.

8. The pharmaceutical composition of claim 2, wherein the compound is of formula (IIb).

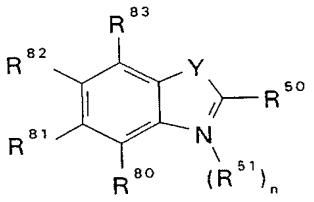
9. The pharmaceutical composition of claim 8, wherein:

R^{15} is methoxycarbonyl or hydroxysulfonyl; R^{16} is selected from hydrogen, ethoxy and methoxy; and R^{17} and R^{18} are each selected from hydrogen and Cl.

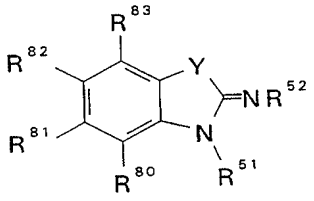
10. The pharmaceutical composition of claim 8, wherein the compound is selected from the group consisting of methyl 2-benzydryl-benzoate, α,α-bis(3,5-dichloro-2-ethoxyphenyl)-ortho-toluenesulfonic acid

sodium salt and *a*,*a*-bis(3,5-dichloro-2-methoxyphenyl)-ortho-toluenesulfonic acid sodium salt.

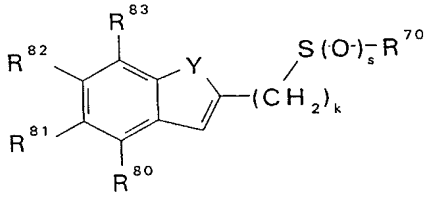
11. The pharmaceutical composition of claim 1, wherein the compound of formula (I) is of formulae (III):



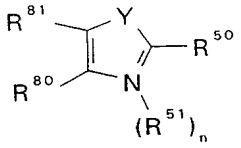
(IIIa)



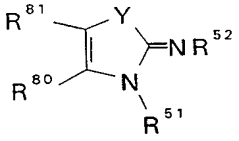
(IIIb)



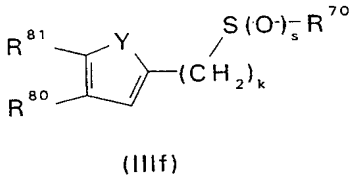
(IIIc)



(IIId)



(IIIe)



(IIIf)

or a pharmaceutically acceptable derivative thereof, wherein:

Y is O, S or NR^{40};

R^{50} is alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, (N-alkyl-, alkenyl-, hydroxyalkyl- or hydroxycarbonylalkyl-heteroarylium)alkyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$ or $NR^{40}R^{41}$;

R^{51} is selected from hydrogen, alkyl, alkenyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

n is 0 or 1;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is selected from aryl, heteroaryl and $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is aryl, heteroaryl or N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene which are unsubstituted or substituted with 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i);

k is 0-6; and s is 0-2.

12. The pharmaceutical composition of claim 11, wherein the compound has formula (IIIa) or (IIId).

13. The pharmaceutical composition of claim 12, wherein:

R^{51} is alkyl, alkenyl, hydroxycarbonylalkyl or hydroxyalkyl; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i).

14. The pharmaceutical composition of claim 12, wherein:

Y is O, S or ethylamino;

R^{50} is selected from 3-(N-propyl-2-benzothiazolium)prop-1-yl, 3-(N-(2-hydroxy-1-ethyl)-2-benzothiazolium)prop-1-yl, 3-(N-(2-propen-1-yl)-2-benzothiazolium)prop-1-yl, 3-(N-(3-hydroxycarbonyl-1-propyl)-2-benzothiazolium)prop-1-yl, 2-(4-dimethylaminophenyl)ethenyl, 3-(N-ocatadecylbenzoxazol-2-inylidene)propenyl, 2-ethyl-3-(N-ethylnaphthothiazol-2-inylidene)propenyl, 2-(N-acetyl-N-phenylamino)ethenyl, (N-methylbenzo-

thiazolin-2-ylidene)aminoazo, 2-(5-(2-(5-chloro-N-ethylbenzothiazolin-2-ylidene)ethylidenyl)-1-diphenylamino-1-cyclopenten-2-yl)ethenyl, 2-hydroxypropenyl, 4-dimethylaminophenyl, 2-methyl-3-(N-ethylnaphthothiazol-2-inylidene)propenyl, (N,N'-dimethylbenzimidazolin-2-ylidene)-aminoazo, 3-(N,N'-diethyl-5-cyanobenzimidazolin-2-ylidene)propenyl, 3-ethoxy-1H-phenalen-1-ylidenemethyl, 3-(N-ethylbenzothiazolin-2-ylidene-2-methyl)propenyl, 3-(N-ethylbenzothiazolin-2-ylidene)propenyl, 5-(N-ethylbenzothiazolin-2-ylidene)pentadienyl, 2-amino-1-naphthylazo, 4-phenylaminophenylazo, pentamethylphenylmethylthio, 4-(bis(2-hydroxyethyl)amino)phenylazo, phenylmethoxy, 4-(3-(4-(N-benzothiazol-2-yl)piperidinyl)propyl)piperidinyl, 2-(4-methylphenylsulfonyl)aminophenyl, benzothiazol-2-yldithio, 3-(N-(2-propen-1-yl)benzothiazolin-2-ylidene)propenyl, 5-(N-propylbenzothiazolin-2-ylidene)pentadienyl and 6-amino-1,4-dihydro-3-cyano-4-(4-cyanophenyl)-benzothiazolin[2,3-a]pyridin-5-yl;

R^{51} is methyl, ethyl, propyl, 2-propen-1-yl, 2-hydroxy-1-ethyl, octadecyl or 3-hydroxycarbonyl-1-propyl; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from hydrogen, methyl, methoxy and Cl; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene and the others are selected as in (i).

15. The pharmaceutical composition of claim 12, wherein the compound is selected from the group consisting of N-ethyl-2-(2-(4-dimethylaminophenyl)ethenyl)naphtho[2,1-d]thiazolium iodide, 3,3'-dioctadecyloxacarbocyanine perchlorate, N-ethyl-2-(2-ethyl-3-(N-ethylnaphtho[1,2-d]thiazolidin-2-ylidene)propenyl)naphtho[1,2-d]thiazolium bromide, N,N'-dioctadecyloxacarbocyanine para-toluenesulfonate, 2-(2-acetanilinovinyl)-3-ethylbenzothiazolium iodide, 3-methyl-2-((3-methyl-2-benzothiazolinylidene)aminoazo)benzothiazolium tetra-

fluoroborate, 5-chloro-N-ethyl-2-(2-(5-(2-(5-chloro-N-ethylbenzothiazolin-2-ylidene)ethylidenyl)-1-diphenylamino-1-cyclopenten-2-yl)ethenyl)benzothiazolium perchlorate, N-ethyl-2-(2-hydroxypropen-1-yl)benzothiazolium chloride, 3,6-dimethyl-2-(4-dimethylaminophenyl)benzothiazolium bromide, N-ethyl-2-(2-methyl-3-(N-ethylnaphtho[1,2-d]thiazolidin-2-ylidene)propenyl)naphtho[1,2-d]thazolium bromide, 2-(4-dimethylamino)-styryl)-3-ethylbenzothiazolium iodide, N-methyl-2-((N,N'-dimethylbenzimidazolin-2-ylidene)aminoazo)benzothiazolium perchlorate, 1-ethyl-2-(3-(N,N'-diethyl-5-cyanobenzimidazolin-2-ylidene)propenyl)-3-(4-hydroxysulfonyl-1-butyl)benzimidazole, 2-(3-ethoxy-1H-phenalen-1-ylidenemethyl)-3-ethylbenzothiazolium tetrafluoroborate, 3,3'-diethyl-9-methylthiacarbocyanine iodide, 3,3'-diethylthiacarbocyanine iodide, 3,3'-diethylthiadicarbocyanine iodide, 3-methyl-2-bromothiazolinone (1,2-dihydro-2-imino-1-naphthylidene)hydrazone hydroiodide, 2-(4-phenylaminophenylazo)-N-methylbenzothiazolium iodide, 2-(pentamethyl-phenyl)methylthiobenzothiazole, 2-(4-(bis(2-hydroxyethyl)amino)phenyl-azo)-7-methoxybenzothiazole, 2-phenylmethoxybenzothiazole, 2-(4-(3-(4-(N-benzothiazol-2-yl)piperidinyl)propyl)piperidinyl)benzothiazole, 2-(2-(4-methylphenylsulfonyl)aminophenyl)naphtho[2,3-d]oxazole, bis(2-benzo-thiazolyl) disulfide, 3,3'-di(2-propen-1-yl)thiacarbocyanine iodide, 3,3'-dipropylthiadicarbocyanine iodide and 2-(6-amino-1,4-dihydro-3-cyano-4-(4-cyanophenyl)-benzothiazolin[2,3-a]pyridin-5-yl)benzothiazole.

16. The pharmaceutical composition of claim 11, wherein the compound is of formula (IIIb) or (IIIe).

17. The pharmaceutical composition of claim 16, wherein:

R^{51} is alkyl; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i).

18. The pharmaceutical composition of claim 16, wherein:

Y is S; R^{51} is methyl or ethyl; R^{52} is (4-nitrophenylazo)(phenyl)-methylimino, 2-imino-5,6-benzo-3-cyclohexen-1-ylimino, 4-dimethylaminophenyl, 3,4-propylenylphenylmethylimino, 1-(3-aminophenyl)ethylimino, 4-dimethylaminophenylmethylimino or 2-nitrophenylsulfonylamino; and R^{80}, R^{81}, R^{82} and R^{83} are all hydrogen.

19. The pharmaceutical composition of claim 16, wherein the compound is selected from the group consisting of 4-nitrophenylazo-benzoyl N-methylbenzothiazolidinone hydrazine bishydrazone, 2-imino-5,6-benzo-3-cyclohexenone N-methylbenzothiazolidinone hydrazine bis-hydrazone, N-ethylbenzothiazolidinone 4-dimethylaminophenylimine, 3,4-propylenylbenzaldehyde N-methylbenzothiazolidinone hydrazine bishydrazone, 3-aminoacetophenone N-methylbenzothiazolidinone hydrazine bis-hydrazone, 4-dimethylaminobenzaldehyde N-methylbenzothiazolidinone hydrazine bishydrazone or N-methylbenzothiazolidinone 2-nitrophenyl-sulfonylhydrazone.

20. The pharmaceutical composition of claim 11, wherein the compound is of formula (IIIc) or (IIIf).

21. The pharmaceutical composition of claim 20, wherein:

Y is O or S;

R^{70} is aryl or heteroaryl; and

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from hydrogen, alkyl, alkoxy, halide, haloalkyl and pseudohalide; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i).

22. The pharmaceutical composition of claim 20, wherein k is 1 and s is 0 or 2.

23. The pharmaceutical composition of claim 20, wherein:

Y is O; R^{70} is aryl; R^{80}, R^{81}, R^{82} and R^{83} are all halide or pseudohalide; k is 1 and s is 0 or 2.

24. The pharmaceutical composition of claim 20, wherein:

Y is O, R^{70} is selected from 3-trifluoromethylphenyl, 4-chlorophenyl and 4-methoxyphenyl; R^{80}, R^{81}, R^{82} and R^{83} are all fluoro; k is 1 and s is 0 or 2.

25. The pharmaceutical composition of claim 20, wherein the compound is selected from the group consisting of 2-(3-trifluoromethyl-phenylthiomethyl)-4,5,6,7-tetrafluorobenz[d]oxazole, 2-(4-chlorophenyl-sulfonylmethyl)-4,5,6,7-tetrafluorobenz[d]oxazole and 2-(4-methoxy-phenylthiomethyl)-4,5,6,7-tetrafluorobenz[d]oxazole.

26. The pharmaceutical composition of claim 1 that is formulated for single dosage administration.

27. The pharmaceutical composition of claim 1 that is formulated for topical or local application to the skin.

28. The pharmaceutical composition of claim 1 that is formulated for intravenous, intramuscular or parenteral administration.

29. The pharmaceutical composition of claim 1 that is formulated for topical or local application to the eye.

30. A method of treating an FGF-mediated disorder, comprising administering to a mammal an effective amount of a compound of formulae (I):

$$Ar^1\text{-}V^1 \quad \text{or} \quad Ar^2 = V^2 \qquad (I)$$

or a pharmaceutically acceptable derivative thereof, wherein:

Ar^1 is a monocyclic or fused bicyclic, tricyclic or tetracyclic aromatic or heteroaromatic group, wherein the heteroaromatic group contains one or two heteroatoms selected from O, S and N;

Ar^2 is a monocyclic or fused bicyclic, tricyclic or tetracyclic arylidene or heteroarylidene group, where the heteroarylidene group contains one or two heteroatoms selected from O, S, and N;

V^1 is selected from the group consisting of diarylalkyl, diheteroarylalkyl, alkenyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$, $NR^{40}R^{41}$ and $-(CH_2)_k-S(O)_s-R^{70}$, where k is 0-6 and s is 0-2;

V^2 is diarylalkylidene, diheteroarylalkylidene or $=NR^{52}$;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is aryl, heteroaryl or $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is selected from aryl, heteroaryl and N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is selected from alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

the aryl, heteroaryl, arylidene and heteroarylidene moieties of the compound of formula (I) are unsubstituted or are substituted with one or more substituents each independently selected from Z; and

Z is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, hydroxysulfonyl, hydroxyphosphoryl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryl-

oxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl, or any two Z groups substituting adjacent atoms may form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene;

wherein the effective amount is sufficient for the prevention or treatment of the FGF-mediated disorder.

31. The method of claim 30, wherein the FGF-mediated disorder is selected from ophthalmic disorders, tumorigenic pathophysiological conditions, rheumatoid arthritis, restenosis, In-Stent restenosis and other vasuclar injury.

32. The method of claim 30, wherein the FGF-mediated disorder is selected from the group consisting of rheumatoid arthritis, Kaposi's sarcoma, restenosis, In-Stent restenosis, FGF-mediated ophthalmic disorders, FGF-mediated dermatological disorders, psoriasis, FGF-mediated tumorigenic pathophysiological conditions, proliferative diabetic retinopathïes, diabetes and melanoma.

33. A method of inhibiting the binding of an FGF peptide to an FGF receptor, comprising contacting the receptor with an FGF peptide and with an effective amount of a compound of formulae (I):

$$Ar^1\text{-}V^1 \quad \text{or} \quad Ar^2 = V^2 \qquad (I)$$

or a pharmaceutically acceptable derivative thereof, wherein:

Ar^1 is a monocyclic or fused bicyclic, tricyclic or tetracyclic aromatic or heteroaromatic group, wherein the heteroaromatic group contains one or two heteroatoms selected from O, S and N;

Ar^2 is a monocyclic or fused bicyclic, tricyclic or tetracyclic arylidene or heteroarylidene group, where the heteroarylidene group contains one or two heteroatoms selected from O, S, and N;

V^1 is selected from the group consisting of diarylalkyl, diheteroarylalkyl, alkenyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$, $NR^{40}R^{41}$ and $-(CH_2)_k-S(O)_s-R^{70}$, where k is 0-6 and s is 0-2;

V^2 is diarylalkylidene, diheteroarylalkylidene or $=NR^{52}$;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is aryl, heteroaryl or $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is selected from aryl, heteroaryl and N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is selected from alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

the aryl, heteroaryl, arylidene and heteroarylidene moieties of the compound of formula (I) are unsubstituted or are substituted with one or more substituents each independently selected from Z; and

Z is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, hydroxysulfonyl, hydroxyphosphoryl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryl-

oxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkyl-aminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl-aminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diaryl-amino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcar-bonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoro-alkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl, or any two Z groups substituting adjacent atoms may form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene;

wherein the contacting is effected prior to, simultaneously with or subsequent to contacting the receptor with the FGF peptide; and the amount is effective to decrease binding of the FGF peptide to the receptor.

34. A method of altering FGF receptor-mediated activity, comprising contacting an FGF receptor with an effective amount of a compound of formulae (I):

$$Ar^1\text{-}V^1 \quad or \quad Ar^2 = V^2 \qquad (I)$$

or a pharmaceutically acceptable derivative thereof, wherein:

Ar^1 is a monocyclic or fused bicyclic, tricyclic or tetracyclic aromatic or heteroaromatic group, wherein the heteroaromatic group contains one or two heteroatoms selected from O, S and N;

Ar^2 is a monocyclic or fused bicyclic, tricyclic or tetracyclic arylidene or heteroarylidene group, where the heteroarylidene group contains one or two heteroatoms selected from O, S, and N;

V^1 is selected from the group consisting of diarylalkyl, diheteroarylalkyl, alkenyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy,

aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$, $NR^{40}R^{41}$ and $-(CH_2)_k-S(O)_s-R^{70}$, where k is 0-6 and s is 0-2;

V^2 is diarylalkylidene, diheteroarylalkylidene or $=NR^{52}$;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is aryl, heteroaryl or $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is selected from aryl, heteroaryl and N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is selected from alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

the aryl, heteroaryl, arylidene and heteroarylidene moieties of the compound of formula (I) are unsubstituted or are substituted with one or more substituents each independently selected from Z; and

Z is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, hydroxysulfonyl, hydroxyphosphoryl, alkyl, haloalkyl, polyhaloalkyl, amino-alkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, aryl-carbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryl-oxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkyl-aminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aryl-aminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diaryl-amino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcar-bonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoro-alkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl,

arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl, or any two Z groups substituting adjacent atoms may form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene;

wherein the mediated activity is altered compared to the activity in the absence of the compound.

35. An article of manufacture comprising packaging material and a compound, contained within the packaging material, wherein the compound is effective for treatment of prevention of an FGF-mediated disorder, the packaging material includes a label that indicates that the compound is used for treatment or prevention of an FGF-mediated disorder, and the compound is of formulae (I):

$$Ar^1\text{-}V^1 \quad \text{or} \quad Ar^2 = V^2 \qquad (I)$$

or a pharmaceutically acceptable derivative thereof, wherein:

Ar^1 is a monocyclic or fused bicyclic, tricyclic or tetracyclic aromatic or heteroaromatic group, wherein the heteroaromatic group contains one or two heteroatoms selected from O, S and N;

Ar^2 is a monocyclic or fused bicyclic, tricyclic or tetracyclic arylidene or heteroarylidene group, where the heteroarylidene group contains one or two heteroatoms selected from O, S, and N;

V^1 is selected from the group consisting of diarylalkyl, diheteroarylalkyl, alkenyl, aryl, heteroaryl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$, $NR^{40}R^{41}$ and $-(CH_2)_k-S(O)_s-R^{70}$, where k is 0-6 and s is 0-2;

V^2 is diarylalkylidene, diheteroarylalkylidene or $=NR^{52}$;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is aryl, heteroaryl or $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is selected from aryl, heteroaryl and N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is selected from alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

the aryl, heteroaryl, arylidene and heteroarylidene moieties of the compound of formula (I) are unsubstituted or are substituted with one or more substituents each independently selected from Z; and

Z is halogen, hydroxy, nitrile, nitro, formyl, mercapto, carboxy, hydroxysulfonyl, hydroxyphosphoryl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, arylalkoxy, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, arylcarbonylamino, aryloxycarbonylamino, azido, alkylthio, arylthio, perfluoroalkylthio, thiocyano, isothiocyano, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl or diarylaminosulfonyl, or any two Z groups substituting adjacent atoms may form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene,

wherein the compound modulates the interaction of an FGF peptide with an FGF receptor.

36. The pharmaceutical composition of claim 2 that is formulated for single dosage administration.

37. The pharmaceutical composition of claim 2 that is formulated for topical or local application to the skin.

38. The pharmaceutical composition of claim 2 that is formulated for intravenous, intramuscular or parenteral administration.

39. The pharmaceutical composition of claim 2 that is formulated for topical or local application to the eye.

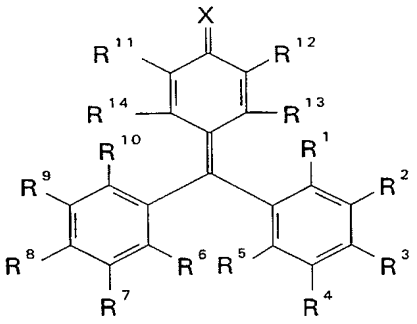
40. The pharmaceutical composition of claim 11 that is formulated for single dosage administration.

41. The pharmaceutical composition of claim 11 that is formulated for topical or local application to the skin.

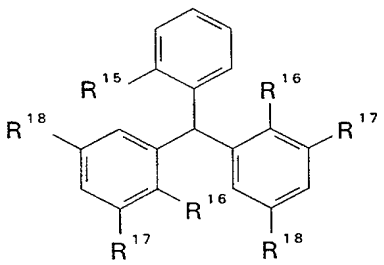
42. The pharmaceutical composition of claim 11 that is formulated for intravenous, intramuscular or parenteral administration.

43. The pharmaceutical composition of claim 11 that is formulated for topical or local application to the eye.

44. The article of manufacture of claim 35, wherein the compound of formulae (I) has formulae (II):



(IIa)



(IIb)

or a pharmaceutically acceptable derivative thereof, where:

R^1 and R^5 are each independently selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$, or, together with R^{13}, form oxy;

R^2 and R^4 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with R^3, form alkylenylamino;

R^3 is hydrogen, hydroxy, thioxy, alkoxy, aryloxy, SR^{40} or $NR^{40}R^{41}$, or, together with R^2 or R^4, forms alkylenylamino;

R^6 and R^{10} are each independently selected from hydrogen, halide, pseudohalide, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$;

R^7 and R^9 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^8 is hydrogen, halide, pseudohalide, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, aryloxy, heteroaryloxy, $NR^{40}R^{41}$, CO_2R^{20}, $PO_3(R^{20})_2$ or SO_nR^{20} where n is 0-3;

R^{11} is selected from hydrogen, halide and pseudohalide, or, together with X, forms alkylenylammonium;

R^{12} is hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with X, forms alkylenylammonium;

R^{13} is hydrogen, or, together with R^1 or R^5, forms oxy;

R^{14} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

X is oxy, thio, NR^{40} or $N^+R^{40}R^{41}$, or, together with R^{11} or R^{12}, forms alkylenylammonium;

R^{15} is CO_2R^{20}, SO_3R^{20} or $PO_3(R^{20})_2$;

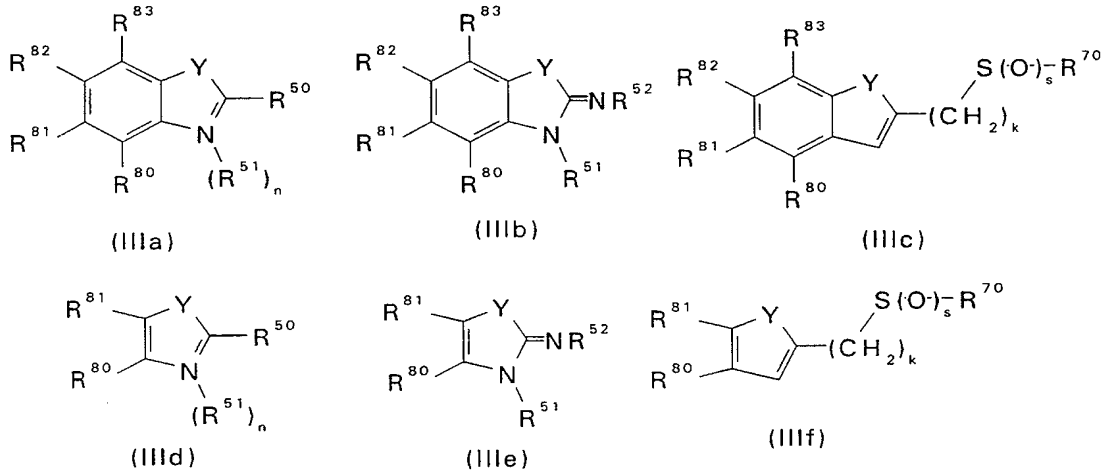
R^{16} is selected from hydrogen, alkoxy, aralkoxy, heteroaralkoxy, aryloxy and heteroaryloxy;

R^{17} and R^{18} are each independently hydrogen, halide or pseudohalide;

R^{20} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl and Na; and

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene.

45. The article of manufacture of claim 35, wherein the compound of formulae (I) has formulae (III):



(IIIa) (IIIb) (IIIc)

(IIId) (IIIe) (IIIf)

or a pharmaceutically acceptable derivative thereof, wherein:

Y is O, S or NR^{40};

R^{50} is alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, (N-alkyl-, alkenyl-, hydroxyalkyl- or hydroxycarbonylalkyl-heteroarylium)alkyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$ or $NR^{40}R^{41}$;

R^{51} is selected from hydrogen, alkyl, alkenyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

n is 0 or 1;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is selected from aryl, heteroaryl and $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is aryl, heteroaryl or N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

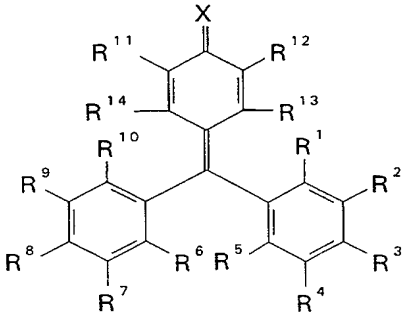
R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z; or

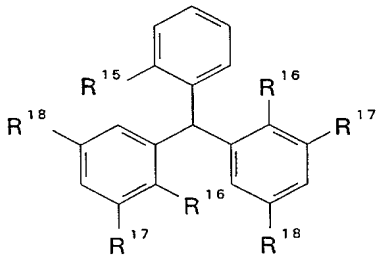
(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene which are unsubstituted or substituted with 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i);

k is 0-6; and s is 0-2.

46. The method of claim 30, wherein the compound of formulae (I) has formulae (II):



(IIa)



(IIb)

or a pharmaceutically acceptable derivative thereof, where:

R^1 and R^5 are each independently selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$, or, together with R^{13}, form oxy;

R^2 and R^4 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with R^3, form alkylenylamino;

R^3 is hydrogen, hydroxy, thioxy, alkoxy, aryloxy, SR^{40} or $NR^{40}R^{41}$, or, together with R^2 or R^4, forms alkylenylamino;

R^6 and R^{10} are each independently selected from hydrogen, halide, pseudohalide, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$;

R^7 and R^9 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^8 is hydrogen, halide, pseudohalide, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, aryloxy, heteroaryloxy, $NR^{40}R^{41}$, CO_2R^{20}, $PO_3(R^{20})_2$ or SO_nR^{20} where n is 0-3;

R^{11} is selected from hydrogen, halide and pseudohalide, or, together with X, forms alkylenylammonium;

R^{12} is hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with X, forms alkylenylammonium;

R^{13} is hydrogen, or, together with R^1 or R^5, forms oxy;

R^{14} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

X is oxy, thio, NR^{40} or $N^+R^{40}R^{41}$, or, together with R^{11} or R^{12}, forms alkylenylammonium;

R^{15} is CO_2R^{20}, SO_3R^{20} or $PO_3(R^{20})_2$;

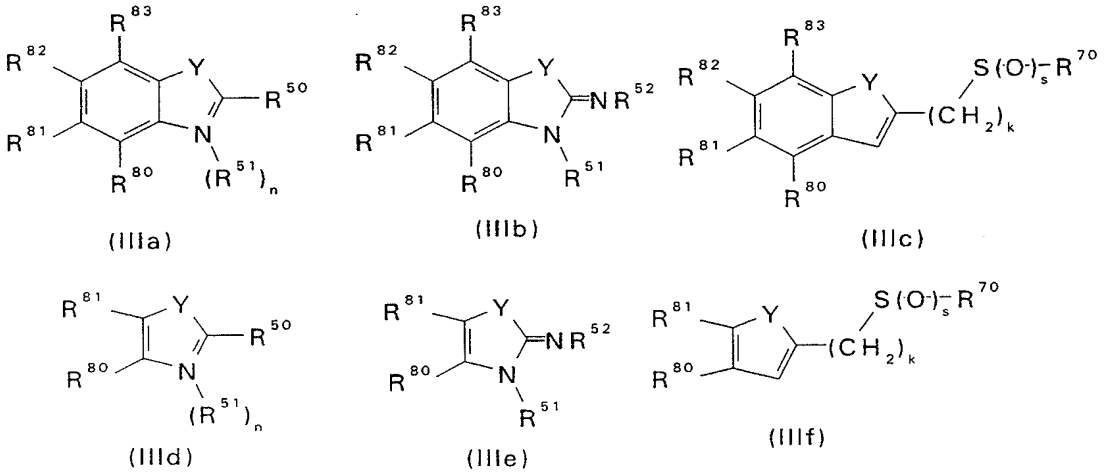
R^{16} is selected from hydrogen, alkoxy, aralkoxy, heteroaralkoxy, aryloxy and heteroaryloxy;

R^{17} and R^{18} are each independently hydrogen, halide or pseudohalide;

R^{20} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl and Na; and

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene.

47. The method of claim 30, wherein the compound of formulae (I) has formulae (III):



(IIIa) (IIIb) (IIIc)

(IIId) (IIIe) (IIIf)

or a pharmaceutically acceptable derivative thereof, wherein:

Y is O, S or NR^{40};

R^{50} is alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, (N-alkyl-, alkenyl-, hydroxyalkyl- or hydroxycarbonylalkyl-heteroarylium)alkyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$ or $NR^{40}R^{41}$;

R^{51} is selected from hydrogen, alkyl, alkenyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

n is 0 or 1;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is selected from aryl, heteroaryl and $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is aryl, heteroaryl or N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

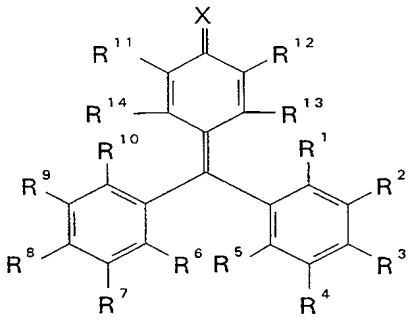
R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z; or

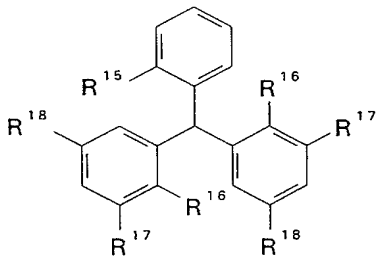
(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene which are unsubstituted or substituted with 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i);

k is 0-6; and s is 0-2.

48. The method of claim 33, wherein the compound of formulae (I) has formulae (II):



(IIa)



(IIb)

or a pharmaceutically acceptable derivative thereof, where:

R^1 and R^5 are each independently selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$, or, together with R^{13}, form oxy;

R^2 and R^4 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with R^3, form alkylenylamino;

R^3 is hydrogen, hydroxy, thioxy, alkoxy, aryloxy, SR^{40} or $NR^{40}R^{41}$, or, together with R^2 or R^4, forms alkylenylamino;

R^6 and R^{10} are each independently selected from hydrogen, halide, pseudohalide, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$;

R^7 and R^9 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^8 is hydrogen, halide, pseudohalide, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, aryloxy, heteroaryloxy, $NR^{40}R^{41}$, CO_2R^{20}, $PO_3(R^{20})_2$ or SO_nR^{20} where n is 0-3;

R^{11} is selected from hydrogen, halide and pseudohalide, or, together with X, forms alkylenylammonium;

R^{12} is hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with X, forms alkylenylammonium;

R^{13} is hydrogen, or, together with R^1 or R^5, forms oxy;

R^{14} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

X is oxy, thio, NR^{40} or $N^+R^{40}R^{41}$, or, together with R^{11} or R^{12}, forms alkylenylammonium;

R^{15} is CO_2R^{20}, SO_3R^{20} or $PO_3(R^{20})_2$;

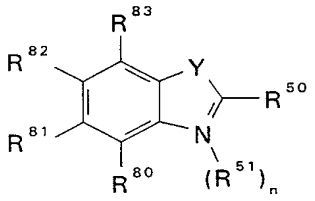
R^{16} is selected from hydrogen, alkoxy, aralkoxy, heteroaralkoxy, aryloxy and heteroaryloxy;

R^{17} and R^{18} are each independently hydrogen, halide or pseudohalide;

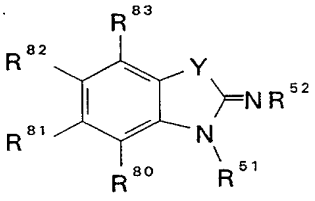
R^{20} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl and Na; and

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene.

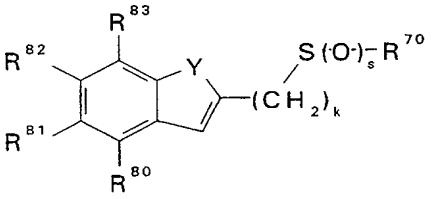
49. The method of claim 33, wherein the compound of formulae (I) has formulae (III):



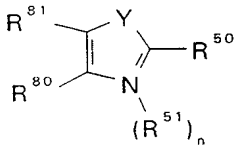
(IIIa)



(IIIb)



(IIIc)



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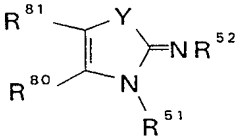
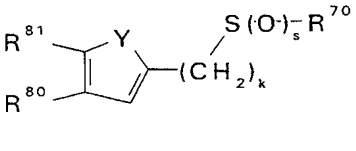


(IIIe)



(IIIf)

or a pharmaceutically acceptable derivative thereof, wherein:

Y is O, S or NR^{40};

R^{50} is alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, (N-alkyl-, alkenyl-, hydroxyalkyl- or hydroxycarbonylalkyl-heteroarylium)alkyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$ or $NR^{40}R^{41}$;

R^{51} is selected from hydrogen, alkyl, alkenyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

n is 0 or 1;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is selected from aryl, heteroaryl and $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is aryl, heteroaryl or N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

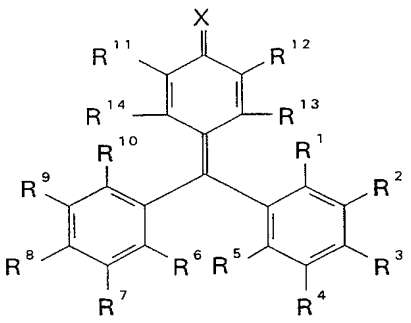
R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z; or

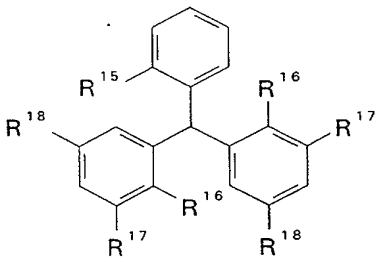
(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene which are unsubstituted or substituted with 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i);

k is 0-6; and s is 0-2.

50. The method of claim 34, wherein the compound of formulae (I) has formulae (II):



(IIa)



(IIb)

or a pharmaceutically acceptable derivative thereof, where:

R^1 and R^5 are each independently selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$, or, together with R^{13}, form oxy;

R^2 and R^4 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with R^3, form alkylenylamino;

R^3 is hydrogen, hydroxy, thioxy, alkoxy, aryloxy, SR^{40} or $NR^{40}R^{41}$, or, together with R^2 or R^4, forms alkylenylamino;

R^6 and R^{10} are each independently selected from hydrogen, halide, pseudohalide, CO_2R^{20}, SO_3R^{20} and $PO_3(R^{20})_2$;

R^7 and R^9 are each independently hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^8 is hydrogen, halide, pseudohalide, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, aryloxy, heteroaryloxy, $NR^{40}R^{41}$, CO_2R^{20}, $PO_3(R^{20})_2$ or SO_nR^{20} where n is 0-3;

R^{11} is selected from hydrogen, halide and pseudohalide, or, together with X, forms alkylenylammonium;

R^{12} is hydrogen, halide, pseudohalide, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or, together with X, forms alkylenylammonium;

R^{13} is hydrogen, or, together with R^1 or R^5, forms oxy;

R^{14} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

X is oxy, thio, NR^{40} or $N^+R^{40}R^{41}$, or, together with R^{11} or R^{12}, forms alkylenylammonium;

R^{15} is CO_2R^{20}, SO_3R^{20} or $PO_3(R^{20})_2$;

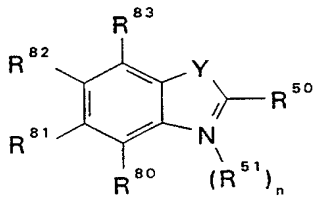
R^{16} is selected from hydrogen, alkoxy, aralkoxy, heteroaralkoxy, aryloxy and heteroaryloxy;

R^{17} and R^{18} are each independently hydrogen, halide or pseudohalide;

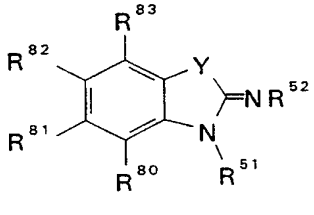
R^{20} is selected from hydrogen, alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl and Na; and

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene.

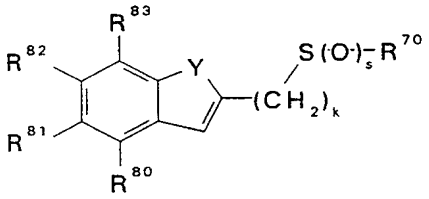
51. The method of claim 34, wherein the compound of formulae (I) has formulae (III):



(IIIa)



(IIIb)



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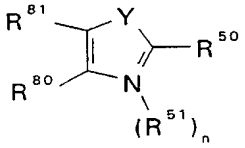

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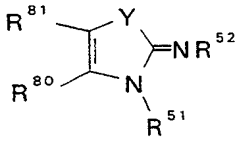

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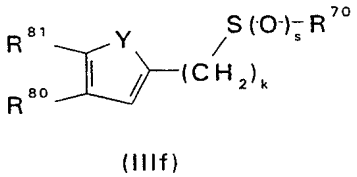

(IIIf)

or a pharmaceutically acceptable derivative thereof, wherein:

Y is O, S or NR^{40};

R^{50} is alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, (N-alkyl-, alkenyl-, hydroxyalkyl- or hydroxycarbonylalkyl-heteroarylium)alkyl, alkoxy, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, SR^{55}, $-N=N-R^{56}$ or $NR^{40}R^{41}$;

R^{51} is selected from hydrogen, alkyl, alkenyl, hydroxycarbonylalkyl, hydroxyalkyl, aralkyl, heteroaralkyl, aryl and heteroaryl;

n is 0 or 1;

R^{40} and R^{41} are each independently hydrogen, alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl, or together form alkylene or alkenylene;

R^{52} is selected from aryl, heteroaryl and $NR^{60}R^{61}$;

R^{55} is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, thioalkyl, thioaralkyl, thioheteroaralkyl, thioaryl or thioheteroaryl;

R^{56} is aryl, heteroaryl or N=heterocyclyl;

R^{60} and R^{61} are each independently hydrogen, aryl, heteroaryl, $S(O)_m$-aryl or $S(O)_m$-heteroaryl, where m is 1 or 2, or together form alkylidene or cycloalkylidene;

R^{70} is alkyl, aralkyl, heteroaralkyl, aryl or heteroaryl;

R^{80}, R^{81}, R^{82} and R^{83} are selected as in (i) or (ii) as follows:

(i) R^{80}, R^{81}, R^{82} and R^{83} are selected from Z; or

(ii) R^{80} and R^{81}, or R^{81} and R^{82}, or R^{82} and R^{83} form 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene which are unsubstituted or substituted with 1,3-butadienylene, 1-aza-1,3-butadienylene or 2-aza-1,3-butadienylene, and the others are selected as in (i);

k is 0-6; and s is 0-2.

SEQUENCE LISTING

(1) GENERAL INFORMATION

(i) APPLICANT:
(A) NAME: Eisai, Ltd.
(B) STREET: 112-88 4-6-10 Koishikawa
(C) CITY: Bunkyo-ku Tokyo
(D) STATE:
(E) COUNTRY: Japan
(F) POSTAL CODE (ZIP):

(i) INVENTOR/APPLICANT:
(A) NAME: Laura Schove
(B) STREET: 1240 Greenlake Drive
(C) CITY: Cardiff
(D) STATE: California
(E) COUNTRY: USA
(F) POSTAL CODE (ZIP): 92007

(i) INVENTOR/APPLICANT:
(A) NAME: Kalyanaraman Ramnarayan
(B) STREET: 11674 Springside Rd.
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(E) COUNTRY: USA
(F) POSTAL CODE (ZIP): 92128

(i) INVENTOR/APPLICANT:
(A) NAME: Venkatachalapathi Yalamoori
(B) STREET: 12246 Summer Breeze Lane
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(D) STATE: California
(E) COUNTRY: USA
(F) POSTAL CODE (ZIP): 92128

(i) INVENTOR/APPLICANT:
(A) NAME: Ming Fai Chan
(B) STREET: 1642 Orchard Wood Road
(C) CITY: Encinitas
(D) STATE: California
(E) COUNTRY: USA
(F) POSTAL CODE (ZIP): 92024

(i) INVENTOR/APPLICANT:
(A) NAME: Vitukudi Narayanaiyengar Balaji
(B) STREET: No. 3 Type 4 CPRI
(C) CITY: Bangalore
(D) STATE:
(E) COUNTRY: India
(F) POSTAL CODE (ZIP): 560 012

(ii) TITLE OF THE INVENTION: ARYL AND HETEROARYL COMPOUNDS USEFUL AS FIBROBLAST GROWTH FACTOR ANTAGONISTS

(iii) NUMBER OF SEQUENCES: 2

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Heller Ehrman White & McAuliffe
(B) STREET: 4250 Executive Square, 7th Floor

(C) CITY: La Jolla
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 92037

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: DOS
(D) SOFTWARE: FastSEQ Version 1.5

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: Herewith
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Seidman, Stephanie L.
(B) REGISTRATION NUMBER: 33,779
(C) REFERENCE/DOCKET NUMBER: 24732-1205PC

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (619) 450-8400
(B) TELEFAX: (619) 450-8499
(C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1440 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:
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(A) NAME/KEY: Coding Sequence
(B) LOCATION: 9...1427
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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Arg Ile Gly Gly Tyr Lys Val Arg Tyr Ala Thr Trp Ser Ile Ile Met
                115                 120                 125

GAC TCT GTG GTG CCC TCT GAC AAG GGC AAC TAC ACC TGC ATT GTG GAG      434
Asp Ser Val Val Pro Ser Asp Lys Gly Asn Tyr Thr Cys Ile Val Glu
            130                 135                 140

AAT GAG TAC GGC AGC ATC AAC CAC ACA TAC CAG CTG GAT GTC GTG GAG      482
Asn Glu Tyr Gly Ser Ile Asn His Thr Tyr Gln Leu Asp Val Val Glu
        145                 150                 155

CGG TCC CCT CAC CGG CCC ATC CTG CAA GCA GGG TTG CCC GCC AAC AAA      530
Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Lys
    160                 165                 170

ACA GTG GCC CTG GGT AGC AAC GTG GAG TTC ATG TGT AAG GTG TAC AGT      578
Thr Val Ala Leu Gly Ser Asn Val Glu Phe Met Cys Lys Val Tyr Ser
175                 180                 185                 190

GAC CCG CAG CCG CAC ATC CAG TGG CTA AAG CAC ATC GAG GTG AAT GGG      626
Asp Pro Gln Pro His Ile Gln Trp Leu Lys His Ile Glu Val Asn Gly
                195                 200                 205

AGC AAG ATT GGC CCA GAC AAC CTG CCT TAT GTC CAG ATC TTG AAG ACT      674
Ser Lys Ile Gly Pro Asp Asn Leu Pro Tyr Val Gln Ile Leu Lys Thr
            210                 215                 220

GCT GGA GTT AAT ACC ACC GAC AAA GAG ATG GAC GTG CTT CAC TTA AGA      722
Ala Gly Val Asn Thr Thr Asp Lys Glu Met Asp Val Leu His Leu Arg
        225                 230                 235

AAT GTC TCC TTT GAG GAC GCA GGG GAG TAT ACG TGC TTG GCG GGT AAC      770
Asn Val Ser Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn
    240                 245                 250

TCT ATC GGA CTC TCC CAT CAC TCT GCA TGG TTG ACC GTT CTG GAA GCC      818
Ser Ile Gly Leu Ser His His Ser Ala Trp Leu Thr Val Leu Glu Ala
255                 260                 265                 270

CTG GAA GAG AGG CCG GCA GTG ATG ACC TCG CCC CTG TAC GTC GAC GCC      866
Leu Glu Glu Arg Pro Ala Val Met Thr Ser Pro Leu Tyr Val Asp Ala
                275                 280                 285
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CGA TTC CCA AGA GGA GCC AGA TCT TAC CAA GTG ATC TGC AGA GAT GAA      914
Arg Phe Pro Arg Gly Ala Arg Ser Tyr Gln Val Ile Cys Arg Asp Glu
            290                 295                 300

AAA ACG CAG ATG ATA TAC CAG CAA CAT CAG TCA TGG CTG CGC CCT GTG      962
Lys Thr Gln Met Ile Tyr Gln Gln His Gln Ser Trp Leu Arg Pro Val
        305                 310                 315

CTC AGA AGC AAC CGG GTG GAA TAT TGC TGG TGC AAC AGT GGC AGG GCA     1010
Leu Arg Ser Asn Arg Val Glu Tyr Cys Trp Cys Asn Ser Gly Arg Ala
    320                 325                 330

CAG TGC CAC TCA GTG CCT GTC AAA AGT TGC AGC GAG CCA AGG TGT TTC     1058
Gln Cys His Ser Val Pro Val Lys Ser Cys Ser Glu Pro Arg Cys Phe
335                 340                 345                 350

AAC GGG GGC ACC TGC CAG CAG GCC CTG TAC TTC TCA GAT TTC GTG TGC     1106
Asn Gly Gly Thr Cys Gln Gln Ala Leu Tyr Phe Ser Asp Phe Val Cys
                355                 360                 365

CAG TGC CCC GAA GGA TTT GCT GGG AAG TGC TGT GAA ATA GAT ACC AGG     1154
Gln Cys Pro Glu Gly Phe Ala Gly Lys Cys Cys Glu Ile Asp Thr Arg
            370                 375                 380

GCC ACG TGC TAC GAG GAC CAG GGC ATC AGC TAC AGG GGC ACG TGG AGC     1202
Ala Thr Cys Tyr Glu Asp Gln Gly Ile Ser Tyr Arg Gly Thr Trp Ser
        385                 390                 395

ACA GCG GAG AGT GGC GCC GAG TGC ACC AAC TGG AAC AGC AGC GCG TTG     1250
Thr Ala Glu Ser Gly Ala Glu Cys Thr Asn Trp Asn Ser Ser Ala Leu
    400                 405                 410

GCC CAG AAG CCC TAC AGC GGG CGG AGG CCA GAC GCC ATC AGG CTG GGC     1298
Ala Gln Lys Pro Tyr Ser Gly Arg Arg Pro Asp Ala Ile Arg Leu Gly
415                 420                 425                 430

CTG GGG AAC CAC AAC TAC TGC AGA AAC CCA GAT CGA GAC TCA AAG CCC     1346
Leu Gly Asn His Asn Tyr Cys Arg Asn Pro Asp Arg Asp Ser Lys Pro
                435                 440                 445

TGG TGC TAC GTC TTT AAG GCG GGG AAG TAC AGC TCA GAG TTC TGC AGC     1394
Trp Cys Tyr Val Phe Lys Ala Gly Lys Tyr Ser Ser Glu Phe Cys Ser
            450                 455                 460

ACC CCT GCC TGC TCT GAG GGA AAC AGT GAC TGA TACTTTGGGA TCC          1440
Thr Pro Ala Cys Ser Glu Gly Asn Ser Asp  *
        465                 470
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 472 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE: internal
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Met Trp Ser Trp Lys Cys Leu Leu Phe Trp Ala Val Leu Val Thr Ala
 1               5                  10                  15
Thr Leu Cys Thr Ala Arg Pro Ser Pro Thr Leu Pro Glu Gln Asp Ala
            20                  25                  30
Leu Pro Ser Ser Glu Asp Asp Asp Asp Asp Asp Asp Ser Ser Ser Glu
        35                  40                  45
Glu Lys Glu Thr Asp Asn Thr Lys Pro Asn Pro Val Ala Pro Tyr Trp
    50                  55                  60
Thr Ser Pro Glu Lys Met Glu Lys Lys Leu His Ala Val Pro Ala Ala
65                  70                  75                  80
Lys Thr Val Lys Phe Lys Cys Pro Ser Ser Gly Thr Pro Asn Pro Thr
                85                  90                  95
Leu Arg Trp Leu Lys Asn Gly Lys Glu Phe Lys Pro Asp His Arg Ile
            100                 105                 110
Gly Gly Tyr Lys Val Arg Tyr Ala Thr Trp Ser Ile Ile Met Asp Ser
        115                 120                 125
Val Val Pro Ser Asp Lys Gly Asn Tyr Thr Cys Ile Val Glu Asn Glu
    130                 135                 140
Tyr Gly Ser Ile Asn His Thr Tyr Gln Leu Asp Val Val Glu Arg Ser
145                 150                 155                 160
Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Lys Thr Val
                165                 170                 175
Ala Leu Gly Ser Asn Val Glu Phe Met Cys Lys Val Tyr Ser Asp Pro
            180                 185                 190
Gln Pro His Ile Gln Trp Leu Lys His Ile Glu Val Asn Gly Ser Lys
        195                 200                 205
Ile Gly Pro Asp Asn Leu Pro Tyr Val Gln Ile Leu Lys Thr Ala Gly
    210                 215                 220
Val Asn Thr Thr Asp Lys Glu Met Asp Val Leu His Leu Arg Asn Val
225                 230                 235                 240
Ser Phe Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile
                245                 250                 255
Gly Leu Ser His His Ser Ala Trp Leu Thr Val Leu Glu Ala Leu Glu
            260                 265                 270
Glu Arg Pro Ala Val Met Thr Ser Pro Leu Tyr Val Asp Ala Arg Phe
        275                 280                 285
Pro Arg Gly Ala Arg Ser Tyr Gln Val Ile Cys Arg Asp Glu Lys Thr
    290                 295                 300
Gln Met Ile Tyr Gln Gln His Gln Ser Trp Leu Arg Pro Val Leu Arg
305                 310                 315                 320
Ser Asn Arg Val Glu Tyr Cys Trp Cys Asn Ser Gly Arg Ala Gln Cys
                325                 330                 335
His Ser Val Pro Val Lys Ser Cys Ser Glu Pro Arg Cys Phe Asn Gly
            340                 345                 350
Gly Thr Cys Gln Gln Ala Leu Tyr Phe Ser Asp Phe Val Cys Gln Cys
        355                 360                 365
Pro Glu Gly Phe Ala Gly Lys Cys Cys Glu Ile Asp Thr Arg Ala Thr
    370                 375                 380
Cys Tyr Glu Asp Gln Gly Ile Ser Tyr Arg Gly Thr Trp Ser Thr Ala
385                 390                 395                 400
Glu Ser Gly Ala Glu Cys Thr Asn Trp Asn Ser Ser Ala Leu Ala Gln
                405                 410                 415
Lys Pro Tyr Ser Gly Arg Arg Pro Asp Ala Ile Arg Leu Gly Leu Gly
            420                 425                 430
Asn His Asn Tyr Cys Arg Asn Pro Asp Arg Asp Ser Lys Pro Trp Cys
        435                 440                 445
Tyr Val Phe Lys Ala Gly Lys Tyr Ser Ser Glu Phe Cys Ser Thr Pro
    450                 455                 460
Ala Cys Ser Glu Gly Asn Ser Asp
465                 470
```

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/24875

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/185 A61K31/425 A61K31/42 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LOZANO, ROSA M. ET AL: "Destabilization, oligomerization and inhibition of the mitogenic activity of acidic fibroblast-growth factor by aurintricarboxylic acid" EUR. J. BIOCHEM. (1997), 248(1), 30-36, XP002122533 the whole document ---	2-10, 26-29, 31,32, 36-39, 44,46, 48,50
X	BENEZRA M ET AL: "Reversal of basic fibroblast growth factor-mediated autocrine cell transformation by aromatic anionic compounds." CANCER RESEARCH, (1992 OCT 15) 52 (20) 5656-62., XP002122534 the whole document ---	2-10, 26-29, 31,32, 36-39, 44,46, 48,50

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 1999	10.03.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. .ial Application No
PCT/US 98/24875

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BENEZRA, MIRIAM ET AL: "Antiproliferative activity to vascular smooth muscle cells and receptor binding of heparin-mimicking polyarom. anionic compounds" ARTERIOSCLER. THROMB. (1994), 14(12), 1992-9, XP002122535 the whole document	2-10, 26-29, 31,32, 36-39, 44,46, 48,50
X	GAGLIARDI A R T ET AL.: "Inhibition of angiogenesis by Aurintricarboxylic acid" ANTICANCER RESEARCH, vol. 13, 1993, pages 475-480, XP002123278 the whole document	2-10, 26-29, 31,32, 36-39, 44,46, 48,50
X	US 5 434 185 A (COLLINS DELWOOD C ET AL) 18 July 1995 (1995-07-18) column 6, line 50 -column 7, line 61 claims column 9, line 56-64 column 12, line 9-16	2-10, 26-29, 31,32, 36-39, 44,46, 48,50
E	WO 98 57922 A (KANEKO HIDEO ;NAKATSUKA IWAO (JP); OOE NORIHISA (JP); MATSUNAGA HA) 23 December 1998 (1998-12-23) the whole document	2-10
A	WO 97 34589 A (ION PHARMACEUTICALS INC ;HARVARD COLLEGE (US); CHILDRENS MEDICAL C) 25 September 1997 (1997-09-25) the whole document	2-10, 26-29, 31,32, 36-39, 44,46, 48,50
E	WO 99 27921 A (EISAI CO LTD) 10 June 1999 (1999-06-10) the whole document	1
E	WO 99 29640 A (BALAJI VITUKUDI NARAYANAIYENGA ;EISAI CO LTD (JP); RAMNARAYAN KALY) 17 June 1999 (1999-06-17) the whole document	1

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna: l Application No
PCT/US 98/24875

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 08240 A (HARVARD COLLEGE ;CHILDRENS MEDICAL CENTER (US)) 21 March 1996 (1996-03-21) claims; example 3 ---	2-10, 26-29, 31,32, 36-39, 44,46, 48,50
X	US 5 189 056 A (ORLANDO ROY C ET AL) 23 February 1993 (1993-02-23) * See Bromophenol blue * ---	2-10, 26-29, 31,32, 36-39, 44,46, 48,50
X	"Merck Index, twelfth edition" 1996 , MERK RESEARCH LABORATORIES XP002122536 * See Magenta I (fuchsine); page 5685, N. 5686 * -----	2-10, 26-29, 31,32, 36-39, 44,46, 48,50

5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 24875

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 46,48,50 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

2-10,36-39,44,46,48,50 complete and 26-29,31-32 partially

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 98/24875

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

01. Claims: 2-10,36-39,44,46,48,50 complete and 26-29,31-32 partially Pharmaceutical compositions comprising compounds defined by Markush formula IIa and IIb (see claim 2) in relation to the treatment and prevention of FGF related diseases.

02 Claims: 11-19,26-29,40-43,45,47,49,51 partial Pharmaceutical compositions comprising compounds defined by Markush formula IIIa, IIIb, IIId, IIIe (see claim 11), having Y= O, in relation to the treatment and prevention of FGF related diseases.

03 Claims: 11-19, 26-29, 31-32, 40-43, 45,47,49,51 partial Pharmaceutical compositions comprising compounds defined by Markush formula IIIa, IIIb, IIId, IIIe (see claim 11), having Y= S, in relation to the treatment and prevention of FGF related diseases.

04. Claims: 11-19,26-29,31-32,40-43,45,47,49,51 partial. As far as not comprised in the previous inventions. Pharmaceutical compositions comprising compounds defined by Markush formula IIIa, IIIb, IIId, IIIe (see claim 11), having Y= NR40, in relation to the treatment and prevention of FGF related diseases.

05. Claims: 11,20-29,31-32,40-43,45,47,49,51 partial. As far as not comprised in the previous inventions. Pharmaceutical compositions comprising compounds defined by Markush formula IIIc, IIIf, (see claim 11), having Y=O, in relation to the treatment and prevention of FGF related diseases.

06. Claims: 11,20-29,31-32,40-43,45,47,49,51 partial. As far as not comprised in the previous inventions. Pharmaceutical compositions comprising compounds defined by Markush formula IIIc, IIIf, (see claim 11), having Y= S, in relation to the treatment and prevention of FGF related diseases.

07. Claims: 11,20-29,31-32,40-43,45,47,49,51 Partial. As far as not comprised in the previous inventions. Pharmaceutical compositions comprising compounds defined by Markush formula IIIc, IIIf, (see claim 11), having Y= NR40, in relation to the treatment and prevention of FGF related diseases.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/24875

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,30,33-35 and part of 2-10,26-29,31-32,36-39,44,46,48,50

In view of the wording of claims 1,30,33-35, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT to such an extent that a meaningful search is impossible.
The present claims 2-10,26-29,31-32,36-39,44,46,48,50 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Moreover, "modulation of the interaction of an FGF peptide with an FGF receptor is not a specified therapeutic application. The search consequently was focused on the specific therapeutic uses mentioned in the description on pages 8-11. Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mentioned in the description, in claims 5, 6, the variants disclosed in claims 26-29 and 31-32 as far as relating to the subject matter of the first invention, and for the general idea underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter.. onal Application No
PCT/US 98/24875

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5434185 A	18-07-1995	AU 678307 B	22-05-1997
		AU 8050294 A	12-12-1994
		CA 2163118 A	24-11-1994
		EP 0699070 A	06-03-1996
		NZ 267802 A	24-04-1997
		WO 9426278 A	24-11-1994
WO 9857922 A	23-12-1998	JP 11071332 A	16-03-1999
WO 9734589 A	25-09-1997	AU 2538897 A	10-10-1997
		CA 2250092 A	25-09-1997
		EP 0918514 A	02-06-1999
WO 9927921 A	10-06-1999	AU 1350699 A	16-06-1999
WO 9929640 A	17-06-1999	AU 1903799 A	28-06-1999
WO 9608240 A	21-03-1996	AU 703863 B	01-04-1999
		AU 3590895 A	29-03-1996
		CA 2200084 A	21-03-1996
		EP 0783303 A	16-07-1997
		JP 10511080 T	27-10-1998
US 5189056 A	23-02-1993	US 5374537 A	20-12-1994